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ARCHIVES OF PATHOLOGY
AND
LABORATORY MEDICINE

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BIOMETRICAL STUDIES IN PATHOLOGY

IV. STATISTICAL CHARACTERISTICS OF A POPULATION COMPOSED OF NECROPSIED PERSONS *

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AND
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The earlier studies in this series [1] were based on a series of cards abstracting the first 5,000 necropsy protocols in the history of the Johns Hopkins Hospital. These cards were prepared prior to the organization of the statistical department of the hospital, and were, so to speak, inherited by it. Several years of work with them demonstrated that they were defective in a number of particulars, to such a degree as to require, for any critical work, almost continued reference back to the original protocols, with a constant great retardation of the progress of any particular investigation.

It was finally decided that it would be the most economical as well as scientifically sound policy, to discard this old series of cards, and to abstract the necropsy protocols de novo on a uniform plan and with critical care. Fortunately, a substantial grant from the National Research Council continued through the academic years 1923-1924 and 1924-1925 furnished the means by which this considerable task could be accomplished.

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* From the Statistical Department of the Johns Hopkins Hospital, Paper No. 7, and from the Institute for Biological Research of the Johns Hopkins University. The investigation on which this paper is based was aided by a grant from the Committee on Human Migration of the National Research Council, for which help we desire to express our gratitude.

† Assisted by Mrs. Margaret McConnell, Miss Blanche F. Pooler and Miss Katie C. Lucas.

1. Pearl, R., and Bacon, A. L.: Biometrical Studies in Pathology. I. The Quantitative Relation of Certain Viscera in Tuberculosis, Johns Hopkins Hospital Rep. **21**:157-230, 1922. Pearl, R.: Biometrical Studies in Pathology. II. Pathometric Index Numbers, Bull. Johns Hopkins Hosp. **33**:406-412, 1922. Pearl, R., and Bacon, A. L.: Biometrical Studies in Pathology. III. The Absolute Weight of the Heart and Spleen in Tuberculous Persons, Johns Hopkins Hosp. Rep. **21**: 297-377, 1924.

We now have a series of cards covering the first 7,500 necropsies in the hospital's history, all of which have been checked twice against the original, and which have been made by the same group of carefully trained and critically supervised workers. These cards will be made the basis of a series of studies of race pathology, of particular disease groups (especially of cancer), and of various other pathologic matters.

It is desirable, as a preliminary to these special studies, at the outstart to make a thorough examination of the general biometric characteristics found in hospital necropsies. Such a study, on a proper statistical scale, has never before been made. It could not be done with the earlier set of cards because of certain statistical defects which they presented as a group. It can now be done, and therefore in the first paper of the series based on the new cards we shall deal with the age distribution and other general demographic characteristics of the necropsies of the Johns Hopkins Hospital population from 1889 to May 22, 1923.

The first necropsy at this hospital was dated May 28, 1889, and was performed by Dr. William H. Welch, the first professor of pathology in the university. Necropsy 7499, the last included in our series of cards, is dated May 22, 1923, and was performed by Dr. M. G. Smith, with added notes in the protocol by Dr. William G. MacCallum, the present professor of pathology. Within this period every necropsy recorded is included in the new card series, except: (*a*) those of premature, still-born infants; (*b*) those in which the brain was the only organ examined; (*c*) those in which there were no records of the sex or color of the individual, and in which no conclusive inference on these points could be drawn from internal evidence presented by the protocol itself; (*d*) those in which only one organ, other than the brain, was examined; (*e*) a small number excluded for incompleteness or inadequacy of the records.

THE CARDS

The new card form is shown in reduced facsimile in figure 1. The size of the card is 21.5 by 28 cm. The upper left hand corner is clipped off to facilitate stacking. They are printed on heavy card stock in four colors, to distinguish readily sex and color: (*a*) white male records on white cards; (*b*) white female records on pink cards; (*c*) colored male records on green cards; (*d*) colored female records on yellow cards.

It is not necessary to discuss in detail the meaning of the several printed items on the card; it is usually evident, and when it is not it will be made so in the special studies which follow. After the cards were printed a number of additional headings were added by rubber stamp or in script on account of the haste necessary in getting out the printed forms.

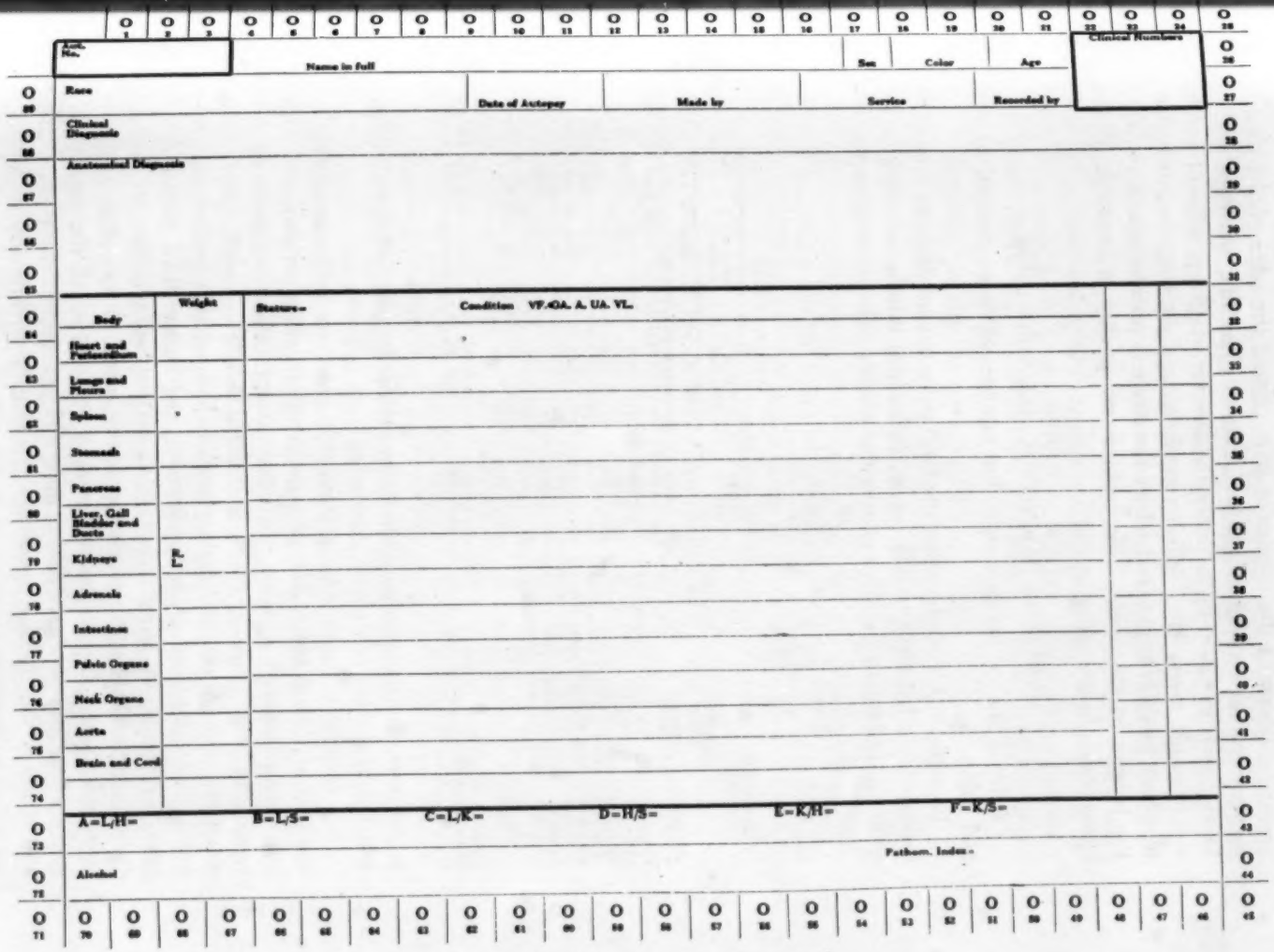

Fig. 1.—Facsimile of new necropsy card.

The purpose of the numbered cells around the edge of the card is to provide the mechanism for the accurate punching of holes with a hand punch in order to facilitate the sorting of like groups of cards; for example, every card which records a case showing any malignant neoplasm has a hole punched where the circle is printed in cell no. 50 at the bottom of the card. This enables one quickly to assemble all the cancer cases in the material.

NUMERICAL MAGNITUDE, SEX AND COLOR

Table 1 shows, by thousands, the number of cases, divided by sex and color.

From table 1 it appears that the necropsies numbered from 1 to 7499 inclusive yielded 6,670 usable cases, 829 serial numbers having to be dropped, for one of the reasons specified above. The missing necropsies

TABLE 1.—*Number of Cases by Date, Sex and Color*

			Number of Cases							
			White Males		White Females		Colored Males		Colored Females	
Necropsy No.	Date of First Necropsy in Group	Date of Last Necropsy in Group	Absolute	Percentage of Total	Absolute	Percentage of Total	Absolute	Percentage of Total	Absolute	Percentage of Total
1- 999	May 28, 1889	Sept. 21, 1897	426	43.6	211	21.6	205	21.0	136	13.9
1000-1999	Sept. 27, 1897	Sept. 22, 1902	370	38.2	182	18.8	250	25.8	166	17.1
2000-2999	Sept. 26, 1902	Jan. 21, 1908	363	39.7	143	15.6	254	27.8	154	16.9
3000-3999	Jan. 22, 1908	Sept. 21, 1913	367	38.6	181	19.2	245	25.8	157	16.5
4000-4999	Sept. 24, 1913	Jan. 20, 1917	340	38.9	168	19.1	216	24.7	149	17.1
5000-5999	Jan. 20, 1917	Sept. 9, 1919	272	34.0	190	23.7	196	24.1	146	18.2
6000-6999	Sept. 10, 1919	May 8, 1922	276	35.5	172	22.1	206	26.5	123	15.8
7000-7499	May 8, 1922	May 22, 1923	177	43.3	73	17.8	81	19.8	78	19.1
Totals			2,591	38.9	1,320	19.8	1,650	24.7	1,109	16.6
Subtotal on color			Total whites = 3,911 = 58.6%				Total colored = 2,759 = 41.4%			
Subtotal on sex			Total males = 4,241 = 63.6%				Total females = 2,429 = 36.4%			

in the present statistics relate chiefly to premature and still-born babies, and fall in the later years of the period.

Of the 6,670 cases, which from this point on will constitute the working statistical basis, 58.6 per cent were of white persons, and 41.4 per cent of colored persons. In the different successive thousands of cases, the proportion of white to colored has in general held fairly constant. During the first eight years of the hospital's history the proportion of necropsies of white persons was higher than during later periods (except the more recent), and correspondingly the proportion of necropsies of colored persons was at the outstart lower than it subsequently became. In relation to sex, 63.6 per cent of all the necropsies in the series have been of males, and 36.4 per cent of females. This proportion is merely an expression of the greater difficulty in getting consent for the necropsy of a female than for that of a male. Curiously enough it seems to have been generally somewhat less easy to get permission for necropsy of colored females than of white females. During

the period from January, 1917, to September, 1919, a peak was attained in the proportion of female to all necropsies, in both white and colored, though during the last years covered in the data the proportion for colored females ran slightly higher.

In relation to time, the number of necropsies per unit of time has tended to increase. Thus during the first period of 7.33 years there were 978 usable necropsies, or approximately 133 per year; during the last two periods, from Sept. 10, 1919, to May 22, 1923, or approximately 3.66 years, there were 1,186 usable necropsies (out of 1,499 numbered protocols), or approximately 324 per year.

A necropsied population represents the end-result of two processes of selection. In the first place, a hospital population is rarely a random sample of the general population from which it is derived. In the case of a charitable foundation, which is what the Johns Hopkins Hospital is essentially, the hospital population will contain a larger proportion of persons from the lower economic strata of society than does the general population. Furthermore, a hospital population tends to include graver cases of illness than random portions of the general population.

TABLE 2.—*The Population of Baltimore by Sex and Color*

	White Males		White Females		Colored Males		Colored Females	
Census Year	Absolute	Percentage of Total	Absolute	Percentage of Total	Absolute	Percentage of Total	Absolute	Percentage of Total
1880	134,446	40.4	144,138	43.4	22,947	6.9	30,782	9.3
1890	176,949	40.7	190,194	43.8	29,165	6.7	38,131	8.8
1900	208,217	40 9	221,482	43.5	35,068	6.9	44,195	8.7
1910	229,141	41.0	244,595	43.8	39,054	7.0	45,695	8.2
1920	308,324	42.0	316,806	43.2	53,236	7.3	55,460	7.6

In the second place, not all persons of the selected hospital population who die come to necropsy. It is often impossible to obtain the consent of relatives, and great effort to obtain consent is not so likely to be made in clinically uninteresting cases as in those which at the moment come nearer to occupying the center of medical discussion and interest.

So altogether it is not to be expected *a priori* that hospital necropsies will be statistically a random sample of those of the general population from which they are drawn. Table 2 shows how the present necropsied population deviates from those of the population of Baltimore (from which in the main they have been derived) in respect to sex and color. This table gives the absolute and percentage distributions of the total population of Baltimore in these respects from 1880 to 1920.

Comparing the percentage columns of table 1 with those of table 2, it is seen that the smallest differences are those in the statistics relative to white males. Roughly, during the whole period this group comes within 2 per cent of being represented in the same proportion in the Johns Hopkins Hospital as in the general population. The white females are greatly under-represented in the hospital necropsy group

as compared with the general population group. In the hospital group there are somewhat less than half as many necropsies on females as there would be if the group were exactly representative of the general population in sex and color. Colored persons are greatly overrepresented in the necropsies; there are about three times too many males and about two times too many females. In making inferences concerning the proportionate incidence of particular pathologic conditions in the general population of Baltimore from relationships found in these necropsies, due account will have to be taken of the disproportions in sex and color distributions which are here shown.

RACE AND AGE DISTRIBUTION

As one of the primary objects of this series of studies is to investigate the influence of racial differences on pathologic phenomena, great pains have been taken in the preparation of the cards to derive from the original clinical and pathologic records as accurate and complete information as possible regarding the racial stock to which the necropsied individual preponderantly or exclusively belonged. The paucity of record of such matters in medical histories has made this a difficult and somewhat unsatisfactory task. Accuracy has been the primary ideal; that is, if a person's name was August Schmidt it was *not* inferred that he was a German, or if the name was Moe Cohen it was *not* inferred that he was a Jew, unless it was specifically stated or made certain by other collateral evidence than the name that the former was a German and the latter a Jew. This meticulous procedure deleted from the several racial groups many cases in which the race stock could be inferred with a high degree of probability; but after this drastic elimination, one can discuss the racial differences with a fair degree of confidence.

When the cards were completed, they were grouped into the following broad racial classes:

I. White American (United States): Persons about whose racial make-up the only obtainable information was that they were white and had been born in this country, generally of native parentage, although the latter point cannot be absolutely certain in every case. Practically speaking, this group means those persons so long resident as a family in the United States that they do not consider their original foreign origin. In ultimate racial composition these people are chiefly mixtures, in quite undeterminable proportions, of English, Irish, Scotch and German stocks.

II. Germanic: Persons definitely recorded as German, Austrian, Dutch, or Swiss, the names indicating that those stated to be Austrian or Swiss were of Germanic origin. Most of the persons in this group were pure German.

III. Slavonic: Czechs, Poles, Russians and Lithuanians.

IV. British: English, Irish, Scotch and Welsh.

V. Scandinavian: Swedes, Norwegians, Danes and Finns.

VI. Mediterranean: French, Italians, Spaniards, Portuguese, Greeks and Cubans.

VII. All other whites: All white persons not included in the foregoing categories, whether such persons had some record as to a particular origin or whether there was no record as to race or nationality. All persons known to be Jews were classified in this group.

VIII. Mulatto: All persons of whom there was a definite record of the embodiment in the individual of a mixture of white and negro stocks.

IX. Colored (negro): All persons of whom the only record was that they were "colored" or "negroes."

Little can be said to commend this classification from the standpoint of even the lowest of anthropologic pedestals. We recognize its defects as clearly as anyone can. But we believe that it is as satisfactory as

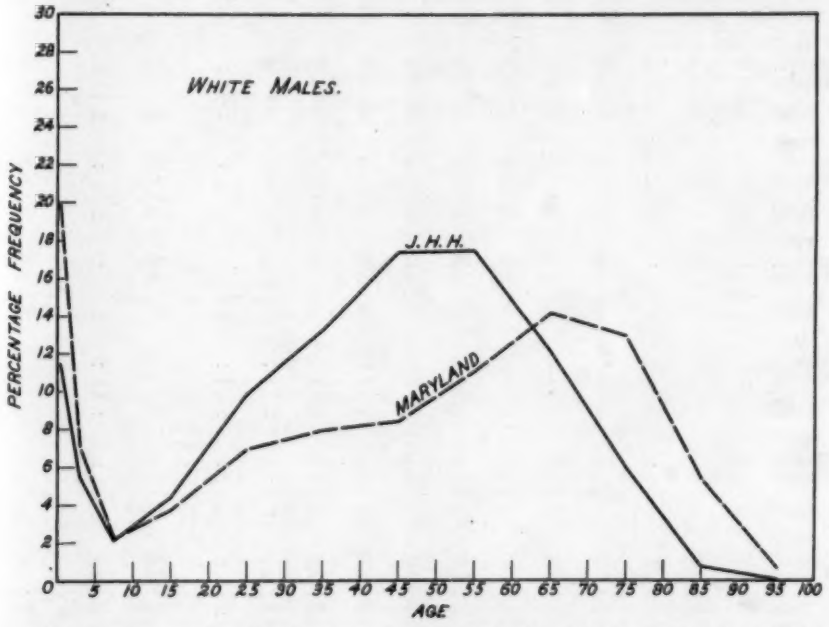

Fig. 2.—Percentage distribution of ages at death of white males in (*a*) this necropsied population (solid line, Johns Hopkins Hospital), and (*b*) the general population of Maryland, average of three years—1900, 1910, and 1920 (broken line, Maryland).

anything that can be done along these lines with the available material. From the standpoint of an anthropologist, there is a shocking paucity of information about race or even nationality in hospital records. From the standpoint of the statistician, it is idle to break up whatever reasonably accurate material there is into a more detailed classification than this, and to end up with distributions so small as to be unusable biometrically. We have given the material careful study from this point of view, and, as already stated, we are convinced that the treatment of it just outlined, is, on the whole, about as good as any that can practically be attained.

Table 3 presents the distribution of the 6,670 cases by racial groups as above defined, sex and age. Table 4 gives the distribution by the same categories, but in percentage instead of absolute values.

TABLE 3.—*Distribution of Necropsy Material by Race, Sex and Age; Absolute Values*

Racial Group and Sex	Age												Total of Known Age	Age Unknown	Grand Total
	Under 1 Yr.	1-4	5-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99			
I															
Male...	214	105	47	75	159	234	264	274	202	91	11	1	1,677	1	1,678
Female	152	108	32	55	102	136	147	85	48	17	..	..	882	2	884
Total	366	213	79	130	261	370	411	359	250	108	11	1	2,559	3	2,562
II															
Male...	2	1	2	10	29	33	77	71	61	28	3	..	317	..	317
Female	1	2	..	6	6	25	29	21	18	3	..	..	111	..	111
Total	3	3	2	16	35	58	106	92	79	31	3	..	428	..	428
III															
Male...	..	..	1	9	17	20	25	8	4	1	..	..	85	..	85
Female	2	..	4	6	7	12	5	3	1	1	..	..	41	..	41
Total	2	..	5	15	24	32	30	11	5	2	..	..	126	..	126
IV															
Male...	..	1	..	3	14	16	25	34	17	9	1	..	120	..	120
Female	..	..	..	1	3	5	5	8	4	..	..	..	26	..	26
Total	..	1	..	4	17	21	30	42	21	9	1	..	146	..	146
V															
Male...	..	..	..	..	7	9	4	6	..	3	..	..	29	..	29
Female	..	..	..	2	2	..	1	..	..	..	..	..	5	..	5
Total	..	..	..	2	9	9	5	6	..	3	..	..	34	..	34
VI															
Male...	1	1	..	1	10	7	6	6	1	2	..	..	35	..	35
Female	1	1	..	2	3	1	..	2	..	..	..	1	11	..	11
Total	2	2	..	3	13	8	6	8	1	2	..	1	46	..	46
VII															
Male...	78	34	4	15	15	18	41	46	26	18	3	..	298	29	327
Female	59	20	3	17	24	31	30	25	12	7	4	..	232	10	242
Total	137	54	7	32	39	49	71	71	38	25	7	..	530	39	569
VIII															
Male...	12	2	1	4	11	12	6	7	3	1	..	..	59	2	61
Female	10	5	2	12	17	10	7	4	1	..	2	..	70	..	70
Total	22	7	3	16	28	22	13	11	4	1	2	..	129	2	131
IX															
Male...	291	129	29	71	246	222	244	199	99	38	7	1	1,576	13	1,589
Female	224	108	31	99	154	159	134	75	33	12	1	1	1,031	8	1,039
Total	515	237	60	170	400	381	378	274	132	50	8	2	2,607	21	2,628
Grand total	1,047	517	156	388	826	960	1,050	874	530	231	32	4	6,605	65	6,670
White															
Males..	295	142	54	113	251	337	442	445	311	153	18	1	2,561	30	2,591
Females	215	131	39	89	147	210	217	144	83	28	4	1	1,308	12	1,320
Total	510	273	93	202	398	547	659	589	394	180	22	2	3,869	42	3,911
Colored															
Males..	303	131	30	75	257	234	250	206	102	39	7	1	1,635	15	1,650
Females	234	113	33	111	171	169	141	79	34	12	3	1	1,101	8	1,109
Total	537	244	63	186	428	403	391	285	136	51	10	2	2,736	23	2,759

From these tables we note, first, the overwhelming preponderance of racial group I (white Americans) among the white people and of group IX (negro) among colored people. Together these two classes comprise nearly 78 per cent of the total material. This means that the

TABLE 4.—*Distribution of Necropsy Material by Race, Sex and Age; Percentage Values*

Racial Group and Sex	Age												Totals of Known Age	Percentage of Total Material
	Under 1 Yr.	1-4	5-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99		
I. Male...	12.8	6.3	2.8	4.5	9.5	14.0	15.7	16.3	12.0	5.4	0.7	0.1	65.5	....
Female	17.2	12.2	3.6	6.2	11.6	15.4	16.7	9.6	5.4	1.9	....	....	34.5	....
Total	14.3	8.3	3.1	5.1	10.2	14.5	16.1	14.0	9.8	4.2	0.4	0.0	100.0	38.7
II. Male...	0.6	0.3	0.6	3.2	9.1	10.4	24.3	22.4	19.2	8.8	0.9	....	74.1	....
Female	0.9	1.8	....	5.4	5.4	22.5	26.1	18.9	16.2	2.7	....	....	25.9	....
Total	0.7	0.7	0.5	3.7	8.2	13.6	24.8	21.5	18.5	7.2	0.7	....	100.0	6.5
III. Male...	....	....	1.1	10.6	20.0	23.5	29.4	9.4	4.7	1.1	....	....	67.5	....
Female	4.9	....	9.8	14.6	17.1	29.3	12.2	7.3	2.4	2.4	....	....	32.5	....
Total	1.6	....	4.0	11.9	19.0	25.4	23.8	8.7	4.0	1.6	....	....	100.0	1.9
IV. Male...	....	0.8	....	2.5	11.7	13.3	20.8	28.3	14.2	7.5	0.8	....	82.2	....
Female	....	....	....	3.8	11.5	19.2	19.2	30.8	15.4	....	....	....	17.8	....
Total	....	0.7	....	2.7	11.6	14.4	20.5	28.8	14.4	6.2	0.7	....	100.0	2.2
V. Male...	....	....	....	....	24.1	31.0	13.8	20.7	....	10.3	....	....	85.3	....
Female	....	....	....	40.0	40.0	....	20.0	....	....	....	....	....	14.7	....
Total	....	....	....	5.9	26.5	26.5	14.7	17.6	....	8.8	....	....	100.0	0.5
VI. Male...	2.9	2.9	....	2.9	28.6	20.0	17.1	17.1	2.9	5.7	....	....	76.1	....
Female	9.0	9.0	....	18.2	27.3	9.0	....	18.2	....	....	....	9.0	23.9	....
Total	4.3	4.3	....	6.5	28.3	17.4	13.0	17.4	2.2	4.3	....	2.2	100.0	0.7
VII. Male...	26.2	11.4	1.3	5.0	5.0	6.0	13.8	15.4	8.7	6.0	1.0	....	56.2	....
Female	25.4	8.6	1.3	7.3	10.3	13.4	12.9	10.8	5.2	3.0	1.7	...	43.8	....
Total	25.8	10.2	1.3	6.0	7.4	9.2	13.4	13.4	7.2	4.7	1.3	....	100.0	8.0
VIII. Male...	35.6	3.3	1.7	6.8	18.6	35.6	10.2	11.9	5.1	1.7	....	....	45.7	....
Female	14.3	7.1	2.9	17.1	24.3	14.3	10.0	5.7	1.4	....	2.9	....	54.3	....
Total	17.1	5.4	2.3	12.4	21.7	17.1	10.1	8.5	3.1	0.8	1.6	....	100.0	2.0
IX. Male...	18.5	8.2	1.8	4.5	15.6	14.1	15.5	12.6	6.3	2.4	0.4	0.1	60.5	....
Female	21.7	10.5	3.0	9.6	14.9	15.4	13.0	7.3	3.2	1.2	0.1	0.1	39.5	....
Total	19.8	9.1	2.3	6.5	15.3	14.6	14.5	10.5	5.1	1.9	0.3	0.1	100.0	39.5
Grand total..	15.9	7.8	2.4	5.9	12.5	14.4	15.9	13.2	8.0	3.5	0.5	0.1	....	100.0
White														
Males...	11.5	5.5	2.1	4.4	9.8	13.2	17.3	17.4	12.1	5.9	0.7	0.04	66.19	38.77
Females	16.4	10.0	3.0	6.8	11.2	16.1	16.6	11.0	6.3	2.1	0.3	0.1	33.81	19.80
Total	13.2	7.1	2.4	5.2	10.3	14.1	17.0	15.2	10.2	4.7	0.6	0.1	100.00	58.58
Colored														
Males...	18.5	8.0	1.8	4.6	15.7	14.3	15.3	12.6	6.2	2.4	0.4	0.06	59.76	24.75
Females	21.3	10.3	3.0	10.1	15.5	15.3	12.8	7.2	3.1	1.1	0.3	0.1	40.24	16.67
Total	19.6	8.9	2.3	6.8	15.6	14.7	14.3	10.4	5.0	1.9	0.3	0.1	100.00	41.42

records in the histories as to race stock are grossly lacking in specificity. Many of the individuals in class IX (negro) belong in class VIII (mulatto), but the absence of any record except "colored" or "negro" in many of the cases makes an accurate classification impossible. The

same is true of the white subjects; more specific information would doubtless transfer some individuals from class I to other white categories. Wherever a specific record concerning race stock has been made in the history, however, it is almost certainly accurate.

The percentage of necropsies on females to total necropsies in the several racial groups varies from 14.7 per cent in group V (Scandinavian) or 17.8 per cent in group IV (British) to 54.3 per cent in group VIII (mulatto).

In the age distributions, it is obvious that infants are greatly underrepresented proportionately in all the racial groups except I, VII, VIII and IX; on the other hand, these four racial groups include together 88.2 per cent of the total material of known age.

TABLE 5.—*Percentage Age Distribution of Deaths from All Causes in Maryland by Sex and Color*

		Age											
Year	Group	Under 1 Yr.	1-4	5-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90 and Over
1900	White males.....	21.3	9.2	2.8	4.3	7.6	8.0	8.5	9.4	12.1	11.4	4.9	0.4
	White females....	19.4	9.3	3.5	4.6	7.8	7.9	7.2	8.5	12.1	12.3	6.2	1.1
	Colored males....	25.5	12.9	3.6	7.6	10.7	7.2	7.6	8.4	7.7	5.4	2.8	0.6
	Colored females..	20.0	11.9	4.6	10.4	12.3	8.9	7.8	7.6	5.8	5.3	3.6	1.8
1910	White males.....	20.6	6.8	1.8	3.6	6.5	8.1	8.5	11.6	14.4	12.6	4.8	0.6
	White females....	17.8	6.9	2.0	4.2	7.1	7.3	7.6	10.1	13.4	14.7	7.8	1.2
	Colored males....	26.3	9.8	2.1	5.7	10.9	9.7	9.0	8.6	8.8	5.9	2.5	0.6
	Colored females..	21.1	9.5	2.4	8.1	11.2	10.0	10.4	8.4	8.4	5.3	3.7	1.4
1920	White males.....	17.9	5.3	2.1	3.3	6.6	7.5	8.1	12.0	15.6	14.7	6.2	0.7
	White females....	15.0	5.4	1.8	3.4	7.8	8.0	8.0	10.5	13.8	16.5	8.5	1.3
	Colored males....	25.0	7.4	1.9	4.6	9.6	10.0	10.2	11.3	9.9	7.3	2.2	0.7
	Colored females..	17.9	7.0	2.0	7.2	12.4	11.6	11.0	11.0	9.5	6.0	3.2	1.1
Total 1900+ 1910+ 1920	White males.....	19.9	7.1	2.2	3.7	6.9	7.9	8.4	11.0	14.1	12.9	5.3	0.6
	White females....	17.3	7.1	2.4	4.1	7.6	7.8	7.6	9.7	13.1	14.5	7.5	1.2
	Colored males....	25.6	10.0	2.5	5.9	10.4	9.0	9.0	9.4	8.8	6.2	2.5	0.7
	Colored females..	19.7	9.5	3.0	8.6	11.9	10.2	9.8	9.0	7.9	5.5	3.5	1.4

In order that a more precise judgment may be formed regarding the age distribution in these necropsies, table 5 is inserted. This table shows the percentage distribution of deaths from all causes at known ages in the general population of Maryland in each of the three years 1900, 1910 and 1920, and for these years taken together, the latter figure being, of course, the average percentage for these years.

Figures 2 to 5 show graphically the differences in tables 4 and 5. These give the percentage frequency distributions by age for white males, white females, colored males and colored females in (*a*) the necropsied population (solid line marked "J. H. H.") and (*b*) deaths from all causes in the general population of Maryland, an average of the years 1900, 1910 and 1920 (broken line, marked "Maryland").

From these diagrams it is evident that all four groups of hospital necropsies deviate, in age distribution, in a similar and characteristic manner from the ages at death from all causes in a fairly comparable

general population. Up to the age of 10 the agreement between the necropsied population and the general population in proportional representation is closer than probably would have been expected. While there are somewhat too few male infants, both white and colored, in the necropsied population, the female infants agree fairly closely in the two populations. There is a considerable excess of necropsied persons from the age of 10 to the age of 50 to 60 or 65 as compared with the age distribution of deaths in the general population. It is followed in the ages from 50 to 60 on to the end of the life span by a corresponding

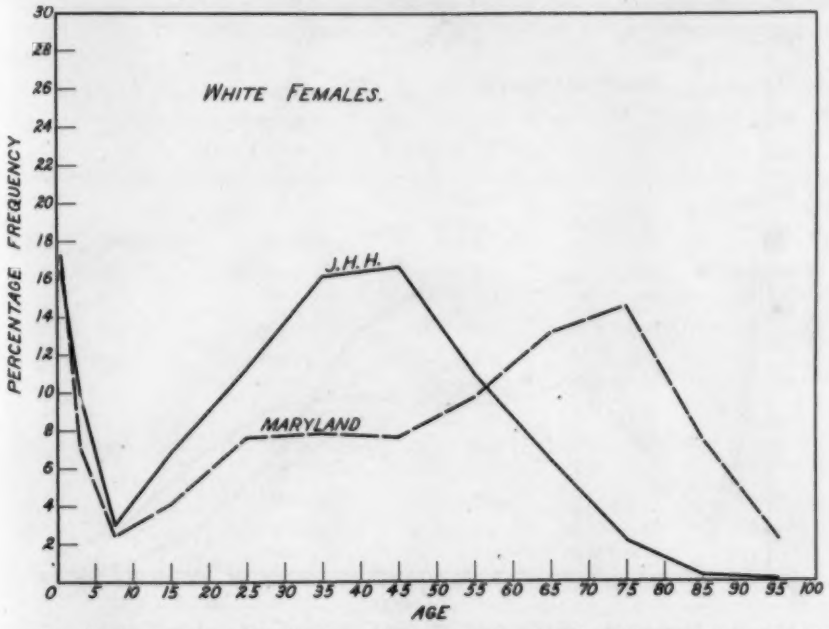

Fig. 3.—Percentage distribution of ages at death of white females in (*a*) this necropsied population (solid line, Johns Hopkins Hospital), and (*b*) the general population of Maryland, average of three years—1900, 1910 and 1920 (broken line, Maryland).

defect in the proportional representation in the necropsied population as compared with the general population.

It appears clearly that this necropsied population cannot be regarded as a fair random sample, in respect to age distribution, of the deaths in the general population from which these subjects came, because it contains proportionately too many young adults and middle aged persons and too few *Greisen*. This is a somewhat discouraging finding to one interested in the general biology of senescence and death, but its explanation seems fairly simple. Old people tend to die at home rather than in a hospital, first, because generally people go to a hospital

to be cured rather than to die, and second, because after a certain age has been reached there is not much hope of effecting a cure. Much less effort is made to save the lives of the old than there is to save the lives of the young, because it is reasoned that every one must die some time, that the old person is probably going to die, and that therefore the best thing to do is to make him as comfortable as possible at home. This attitude toward the aged and infirm goes back to the most primitive conditions of human existence, when to care for the aged and infirm involved a definite elimination risk to the young and healthy in the

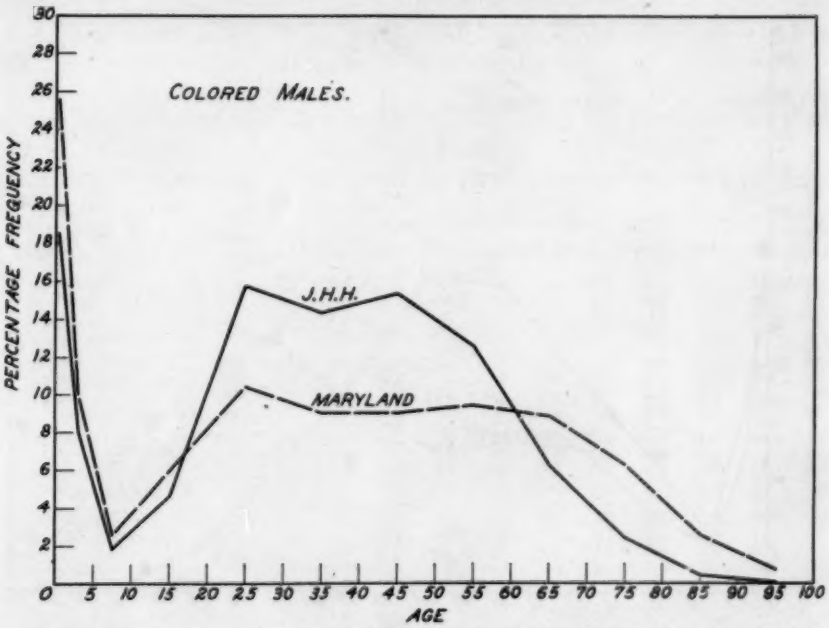

Fig. 4.—Percentage distribution of ages at death of colored males in (*a*) this necropsied population (solid line, Johns Hopkins Hospital), and (*b*) the general population of Maryland, average for three years—1900, 1910 and 1920 (broken line, Maryland).

struggle for existence. So far as concerns the old person himself, this custom is not biologically sound. Medical literature abounds with cases of extremely old persons making excellent recoveries from major surgical operations, and of cases of old people responding to energetic medical treatment in the most gratifying manner.[2] In the material on

2. The following few citations merely illustrate the point. It could, if it were worth while, be documented to almost any desired extent. Ronaldson, G. W.: Diphtheria in Old Age, Brit. M. J. **1**:733, 1925. Bernstein, G.: Long Survival with Cancer of the Breast, ibid., p. 734. Thompson, R. J. C., and Todd, R. E.: Senescence and Senility, Lancet **1**:874-1877, 1922. Old Age and Blood Pressure Problems, ibid. **2**:503, 1922.

longevity in the archives of the Institute for Biological Research of this university there is a great deal of evidence in support of this point.

The characteristic deviation of the necropsied from the general population, which has been exhibited graphically, is also reflected in the biometric constants, shown in table 6.

From table 6 it will be noted that, in the first place, the mean ages at death of males on whom necropsies have been made, whether white or colored, differ from the mean ages at death of the corresponding moiety of the general population of Maryland by insignificant amounts, taking into consideration the probable errors of the differences. This result arises from the compensatory effect, so far as concerns the means,

TABLE 6.—*Biometric Constants for Age of the Necropsied Population by Sex and Color Compared with Deaths from All Causes in Maryland for the Years 1900, 1910 and 1920 Combined*

Group	Population	Mean, Years	Standard Deviation, Years	Coefficient of Variation, per Cent
White males.....	Necropsies	38.46 ± 0.31	23.12 ± 0.22	60.1 ± 0.7
	Maryland	39.25 ± 0.13	29.52 ± 0.09	75.2 ± 0.3
	Difference	−0.79 ± 0.34	−6.40 ± 0.24	−15.1 ± 0.8
White females.....	Necropsies	29.67 ± 0.41	22.21 ± 0.29	74.9 ± 1.4
	Maryland	41.39 ± 0.14	30.18 ± 0.10	72.9 ± 0.3
	Difference	−11.72 ± 0.43	−7.97 ± 0.31	+2.0 ± 1.4
Colored males.....	Necropsies	30.19 ± 0.37	22.36 ± 0.26	74.1 ± 1.3
	Maryland	29.57 ± 0.21	27.27 ± 0.15	92.2 ± 0.8
	Difference	+0.62 ± 0.43	−4.91 ± 0.30	−18.1 ± 1.5
Colored females.....	Necropsies	24.15 ± 0.42	20.44 ± 0.29	84.6 ± 1.9
	Maryland	31.35 ± 0.21	27.09 ± 0.15	86.4 ± 0.7
	Difference	−7.20 ± 0.47	−6.65 ± 0.33	−1.8 ± 2.0

of the differences between the distributions in the different parts of the age scale. In variability, whether measured by standard deviation or coefficient of variation, the males of the necropsied population, both white and colored, fall significantly below the corresponding groups of the general population. This would be expected *a priori* from the fact that the necropsied population is the resultant of a process of selection.

In the case of the females, both white and colored, the mean ages at death fall significantly earlier in those on whom necropsies were performed than in the general population. As measured by the standard deviation, the variation in age at death is significantly smaller in the female necropsy groups than it is in the corresponding parts of the general population. The coefficients of variation, however, owing to the corresponding differences in the mean already mentioned, have values not significantly different in the female necropsy subjects and in

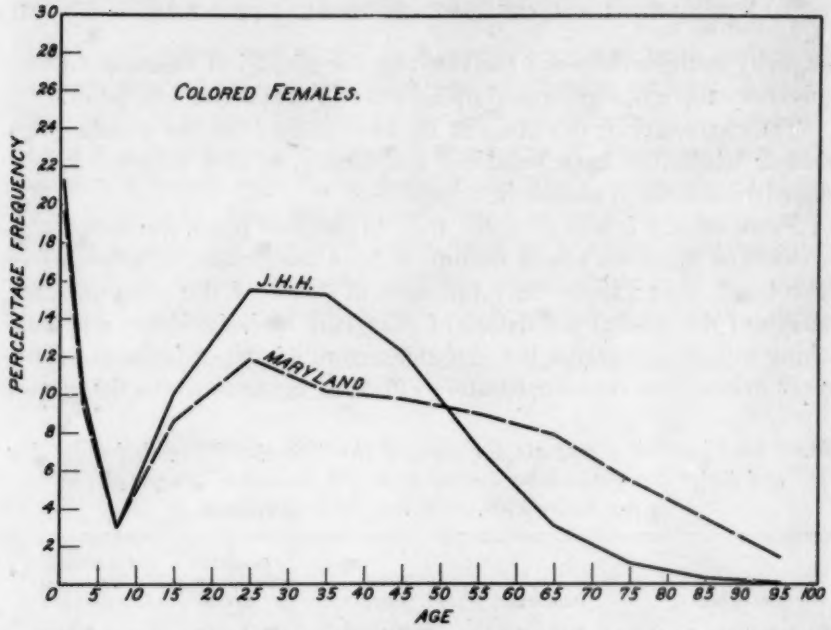

Fig. 5.—Percentage distribution of ages at death of colored females in (*a*) this necropsied population (solid line, Johns Hopkins Hospital), and (*b*) the general population of Maryland, average of three years—1900, 1910 and 1920 (broken line, Maryland).

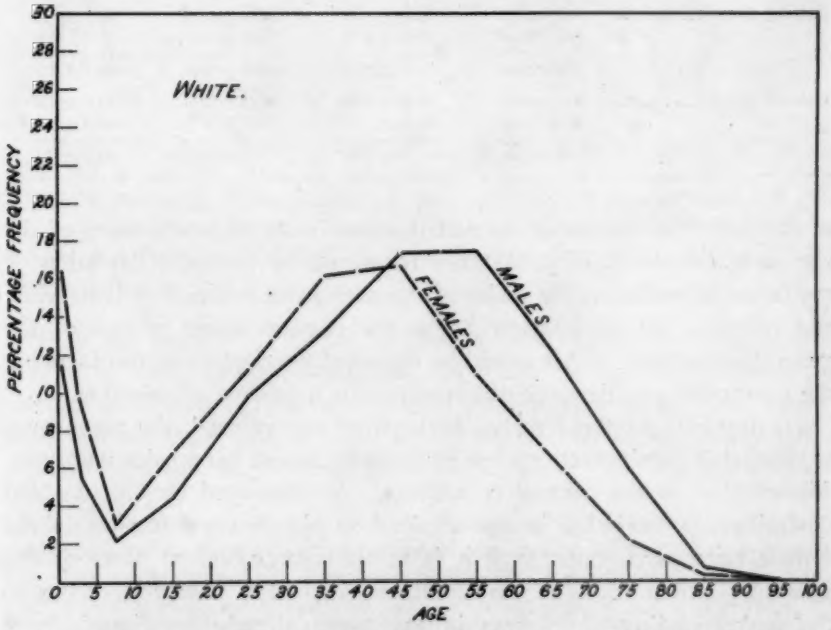

Fig. 6.—The percentage age distribution of males (solid line) and females (broken line) in the whites in this collection of hospital necropsies.

the general population. In this case the standard deviation is to be regarded as a truer measure of variation than is the coefficient of variation.

The characteristic differences in respect to age distribution between the sexes in the necropsied population are shown graphically in figures 6 and 7.

In both the white and colored persons there are proportionately more females than males at early ages. This excess of females continues up to the age of 40 in the case of white persons and to about the age of 20 in colored persons. From about the age of 40 on as far as the distributions go, in both white and colored persons, there are proportionately more male than female necropsies. At some of the ages the sex difference in proportional frequency is insignificant statistically, but the general trends are as indicated.

The differences between the sexes in age distribution, shown in figures 6 and 7, are reflected in the biometric constants of table 6. We have the following system of differences:

TABLE 7.—*Difference in Age Between Males and Females in This Necropsied Population*

White Persons			Colored Persons		
Mean	Standard Deviation	Coefficient of Variation	Mean	Standard Deviation	Coefficient of Variation
$+8.79 \pm 0.51$	$+0.91 \pm 0.36$	-14.8 ± 1.6	$+6.04 \pm 0.56$	$+1.92 \pm 0.39$	-10.5 ± 2.3

In this experience the mean age at death of the males is significantly higher than that of the females. This is the opposite of the relation usually observed in the mortality statistics of general populations. It marks clearly one respect in which this necropsied population differs statistically from a general population. In absolute variation, as measured by the standard deviation, the age at death of males varies more than that of females. The difference is statistically significant in the case of colored persons, and probably so in case of the white persons. In proportion to the mean ages at death, the females are more variable than are the males, but it is probably misleading to refer the variation to the mean in this case.

The characteristic differences in respect to age distribution between white and colored persons in the necropsied population are shown in figures 8 and 9.

In this experience there is a general tendency (with some trifling exceptions) toward a relative excess of colored persons as compared with white persons, up to about the ages of 35 to 40, and a relative defect of colored persons at higher ages. This relation is true of both the male and the female portions of this necropsied population. It is probably partly the result of the selective processes in the formation of

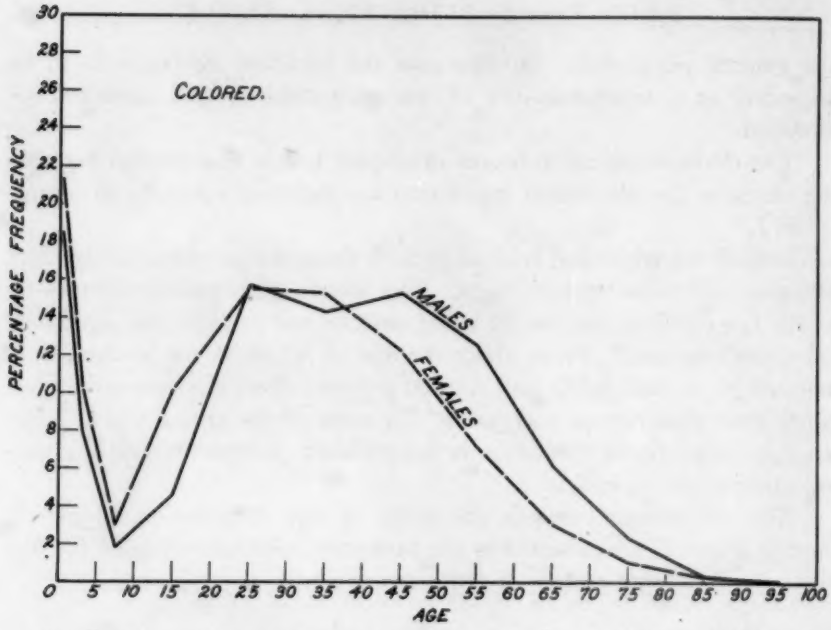

Fig. 7.—The percentage of age distribution of males (solid line) and females (broken line) in the colored persons in this collection of hospital necropsies.

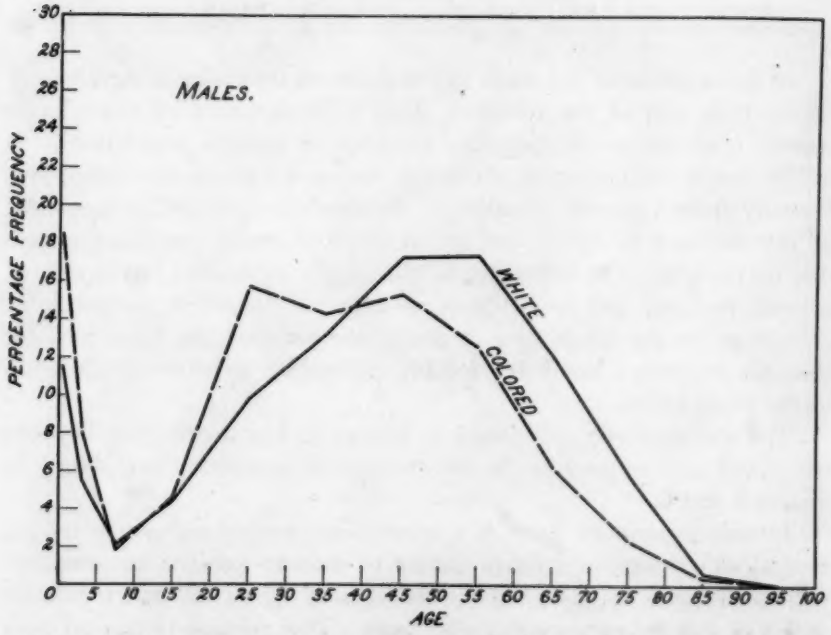

Fig. 8.—The percentage age distribution of white (solid line) and colored (broken line) males in this collection of hospital necropsies.

a necropsied population already discussed, but may also in part reflect the lower age at death generally found in colored as compared with white populations.

From table 6 we have the following differences between white and colored persons:

TABLE 8.—*Differences in Age Between White and Colored Subjects in This Necropsied Population*

White Persons			Colored Persons		
Mean	Standard Deviation	Coefficient of Variation	Mean	Standard Deviation	Coefficient of Variation
+8.27 ± 0.48	+0.76 ± 0.34	−14.0 ± 1.5	+5.52 ± 0.59	+1.77 ± 0.41	−9.7 ± 2.4

TABLE 9.—*Sex Differences in Age at Death in the Different Racial Groups*

Racial Group	Sex	Mean, Years	Standard Deviation, Years	Coefficient of Variation, per Cent
I. U. S. A., white	Male	37.03 ± 0.39	23.56 ± 0.27	63.6 ± 1.0
	Female	27.58 ± 0.50	21.86 ± 0.35	79.3 ± 1.9
	Difference	+9.45 ± 0.63	+1.70 ± 0.44	−15.7 ± 2.1
II. Germanic	Male	49.80 ± 0.62	16.34 ± 0.44	32.8 ± 1.0
	Female	44.88 ± 1.00	15.62 ± 0.71	34.8 ± 1.8
	Difference	+4.92 ± 1.18	+0.72 ± 0.83	−2.0 ± 2.1
III. Slavonic	Male	37.42 ± 1.00	13.65 ± 0.71	36.5 ± 2.1
	Female	30.40 ± 1.77	16.84 ± 1.25	55.4 ± 5.2
	Difference	+7.02 ± 2.02	−3.19 ± 1.44	−18.9 ± 5.6
IV. British	Male	48.63 ± 0.96	15.60 ± 0.68	32.1 ± 1.5
	Female	45.84 ± 1.79	13.54 ± 1.27	29.5 ± 3.0
	Difference	+2.79 ± 2.06	+2.06 ± 1.44	+2.6 ± 3.4
V. Scandinavian	Male	42.40 ± 1.88	15.01 ± 1.33	35.4 ± 3.5
	Female	25.07 ± 3.19	10.57 ± 2.25	42.2 ± 10.4
	Difference	+17.33 ± 3.70	+4.44 ± 2.61	−6.8 ± 11.0
VI. Mediterranean	Male	38.08 ± 1.95	17.08 ± 1.38	44.9 ± 4.3
	Female	31.63 ± 5.34	26.25 ± 3.77	83.0 ± 18.6
	Difference	+6.45 ± 5.65	−9.17 ± 4.00	−38.1 ± 19.1
VII. All other whites	Male	30.40 ± 1.05	26.87 ± 0.74	88.4 ± 3.9
	Female	27.58 ± 1.07	24.11 ± 0.75	87.4 ± 4.4
	Difference	+2.82 ± 1.48	+2.76 ± 1.05	+1.0 ± 5.9
VIII. Mulatto	Male	28.86 ± 1.81	20.61 ± 1.28	71.4 ± 6.3
	Female	25.08 ± 1.56	19.37 ± 1.10	77.2 ± 6.5
	Difference	+3.78 ± 2.38	+1.25 ± 1.68	−5.8 ± 9.1
IX. Negro	Male	30.24 ± 0.38	22.42 ± 0.27	74.1 ± 1.3
	Female	24.08 ± 0.43	20.51 ± 0.30	85.1 ± 2.0
	Difference	+6.16 ± 0.57	+1.91 ± 0.40	−11.0 ± 2.4

Presumably merely by a coincidence, the differences in the constants of their age distributions between necropsies of white and colored persons are of the same order of magnitude and in the same sense as those between males and females. The white persons that come to necropsy are significantly older at death than the colored persons.

TABLE 10.—*Changes in Mean Ages at Death in Groups I and IX of Necropsy Subjects*

Serial Numbers	Racial Group		Racial Group IX	
	Males	Females	Males	Females
1- 999	42.66 ± 0.76	38.85 ± 0.92	41.88 ± 0.79	36.01 ± 1.01
1000-1999	41.51 ± 0.83	37.96 ± 1.16	40.91 ± 0.81	36.95 ± 1.02
2000-2999	44.15 ± 0.90	37.63 ± 1.59	43.90 ± 0.77	36.88 ± 1.11
3000-3999	40.16 ± 0.98	29.25 ± 1.17	35.71 ± 0.92	28.18 ± 1.06
4000-4999	35.28 ± 1.10	24.34 ± 1.37	23.85 ± 1.08	16.44 ± 1.08
5000-5999	28.75 ± 1.24	17.89 ± 1.19	15.87 ± 1.02	10.54 ± 0.88
6000-6999	30.95 ± 1.28	23.47 ± 1.48	29.93 ± 1.14	17.60 ± 1.19
7000-7999	30.50 ± 1.47	19.11 ± 1.77	16.31 ± 1.72	16.46 ± 1.49

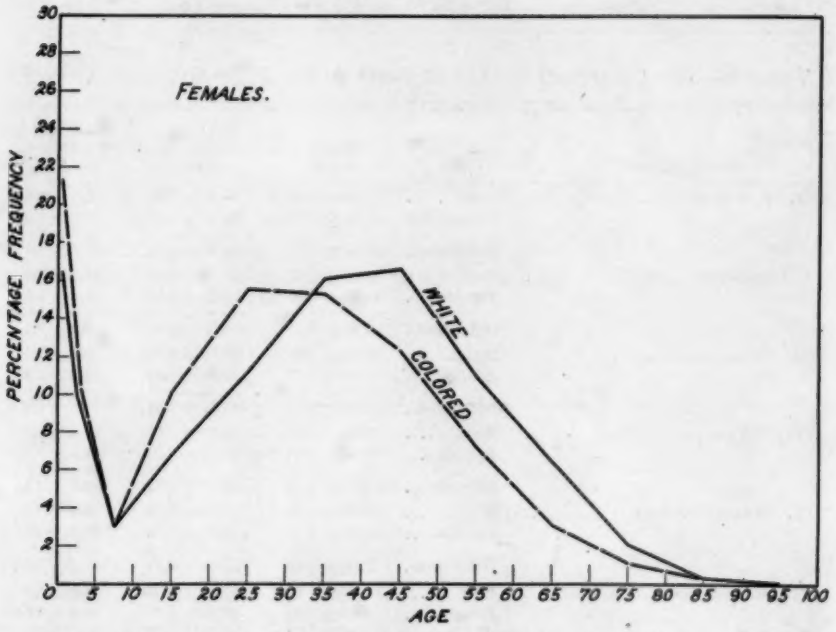

Fig. 9.—The percentage age distribution of white (solid line) and colored (broken line) females in this collection of hospital necropsies.

Table 9 exhibits the biometric constants for the age distributions of the different racial groups in the material by sex.

There are some considerable differences in mean age at death between different racial groups in this necropsied population. Group II (Germanic) shows the highest mean age at death in males, and group VIII (mulatto) the lowest. Among the females the highest mean age at death is in group IV (British), but there is no significant difference between the mean for females of this group and that of females of group II. The differences in mean age at death in the different racial groups are in large part due to the relative frequency of necropsies of infants. In all the racial groups the mean age at death of the males is

higher than that of the females. The sex differences are significant, having regard to the probable errors in groups I, II, III and V only.

Necropsies of infants have increased considerably during recent years. This is shown in the frequency distributions of tables 3 and 4, and in table 10, which gives the mean age at death in successive thousands of necropsy serial numbers for racial groups I and IX.

SUMMARY

In this paper is presented a detailed account of the biometric characteristics of the age, sex and racial distributions of persons included in the necropsy records of the Johns Hopkins Hospital numbered from 1 to 7499. A detailed discussion is given of the manner in which the distributions differ among themselves and from those of the general population from which these necropsy subjects mainly come. The data presented afford the requisite statistical basis for special biometric studies of particular pathologic conditions. Any conclusions derived from this material must for the present be regarded as peculiar to the necropsies of the Johns Hopkins Hospital. Owing to the special nature and mode of formation of a necropsied population, demographically speaking, it is impossible to generalize from the experience of a single hospital, except within special and carefully defined limits.

COMPENSATORY HYPERTROPHY AND HYPERPLASIA OF THE ISLANDS OF LANGERHANS IN THE PANCREAS OF A CHILD BORN OF A DIABETIC MOTHER*

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AND

L. C. FEEMSTER, M.D.

ST. LOUIS

A case which we recently observed at Barnes Hospital strongly suggests compensatory hypertrophy and hyperplasia of the islands of Langerhans in a fetus born of a diabetic mother. It is probable that the increase in fetal insular tissue may compensate in the later months of pregnancy for a deficiency of the islands of Langerhans in the mother, but at the same time this compensatory hypertrophy may lead to pathologic conditions in the new-born.

So far as we are aware, this is the first time that such a sequence has been observed in this completeness, although some other observations corroborate the conclusions which we have drawn. We give briefly the clinical history of this case.

REPORT OF CASE

MOTHER.—*History.*—M. C., White, aged 44, was admitted to Barnes Hospital, Aug. 24, 1924, because of swelling of the feet, weakness, headache, gastric disturbances and inability to remain sugar-free on a diet of 2,200 calories and 35 units of insulin daily. This was her sixth pregnancy. Four children whose ages varied between 26 and 15 were alive. The fifth pregnancy, five years before, was terminated artificially at three months because of diabetes mellitus.

The patient had had diabetes mellitus for fifteen years, during the last ten of which she had been under observation at Barnes Hospital. Her first admission was in October, 1915, for glycosuria, pain in the back and profuse menstruation. Since then she had been admitted in February, 1919, for a curettage; June, 1921, for edema; April, 1923, for postinfluenzal acidosis; September, 1923, for cystitis and right hydronephrosis. Each time she showed hyperglycemia and glycosuria, and except in September, 1923, a positive test for acetone. On April 26, 1924, the patient was admitted because of pregnancy. She had not menstruated since Jan. 10, 1924. In view of the advanced stage of pregnancy, it was decided to allow her to go to term. She was excreting 14 gm. of sugar daily. On a diet of 1,800 calories and 30 units of insulin daily she was discharged. Following her discharge she developed edema of the ankles and vomited frequently.

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Second Admission.—She was readmitted, Aug. 24, 1924. Physical examination now was essentially negative, except for the marked edema of her feet and legs. The fundus of the uterus was well above the umbilicus. The heart was enlarged to the left and downward. Urinalysis on admission revealed: specific gravity, 1.025; albumin, ++++; ferric chlorid, atypical; sugar, ++; few granular casts and many white blood cells. There were 110 mg. of blood sugar.

Treatment and Course.—She was placed on a diet yielding 2,090 calories. Forty units of insulin were administered daily. Under this treatment, the patient was sugar-free. The insulin was gradually reduced to 25 units by September 3, when the blood sugar was 117 mg. On September 10, the blood sugar was 105 mg. on a diet of 2,284 calories. One week later, the blood sugar was 0.096 mg.

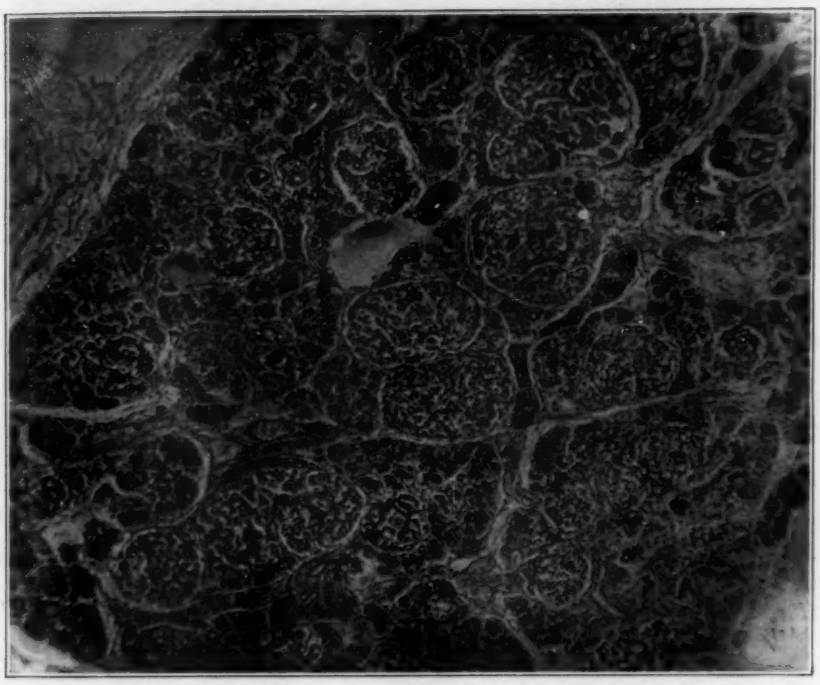

Fig. 1.—A photomicrograph, medium power, of a section of pancreas mainly composed of islands of Langerhans, which are grealty hypertrophied. Between the islands some acinar tissue is seen.

on 20 units of insulin with the same diet. The insulin was then reduced to 15 and subsequently to 10 units on September 20. Sugar now appeared in the urine for the first time. The insulin was therefore increased to 15 units, and the glycosuria disappeared. On Sept. 23, 1924, the patient went into labor, which lasted only five hours, and was delivered easily of a female infant. The blood sugar two hours after delivery was 225 mg. On September 25, the blood sugar was increased to 107 mg. on 20 units of insulin and a diet of 2,241 calories. The urine contained 4.9 gm. of sugar. Daily readings of the blood pressure varied from 190 systolic and 100 diastolic on admission to 165 systolic and 100 diastolic on Sep-

tember 26. At the time of delivery, the blood pressure was 210 systolic and 120 diastolic, but it fell to 145 systolic and 90 diastolic, and was fairly constant at 160 systolic and 95 diastolic until death.

The puerperium was normal until Sept. 28, 1924, 8 p. m., when the patient awoke from a sound sleep complaining of a smothering sensation. She gasped for breath, and began to exude a white froth from her nose and mouth; she became cyanotic, and the pulse was rapid and shallow. She died at 8:20 p. m. in spite of stimulant treatment. There were signs of fluid in the lungs just before death.

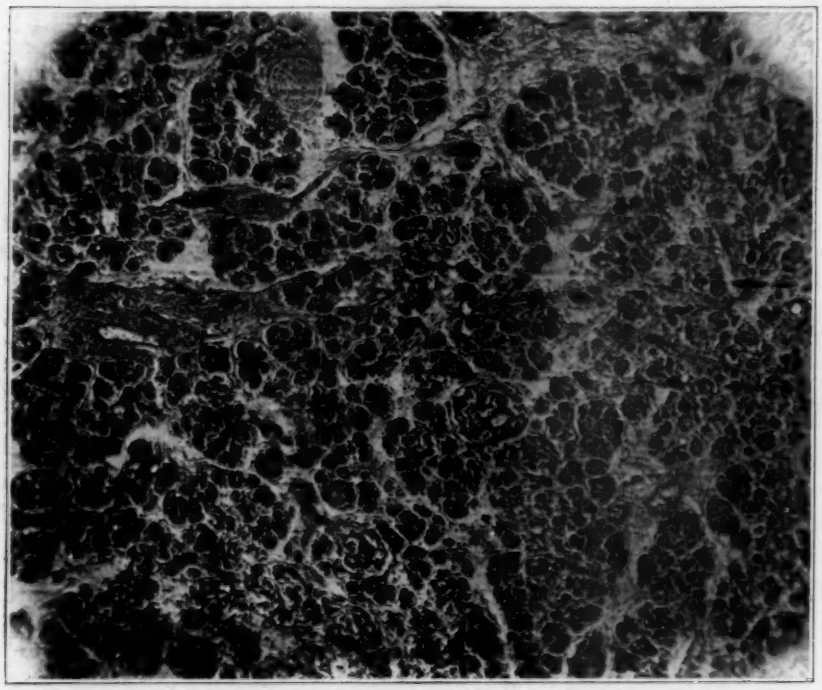

Fig. 2.—With slightly higher magnification than fig. 1, a photomicrograph of normal pancreas of child of same age. The number and size of islands are considerably smaller than in the preceding picture.

The clinical diagnosis was: diabetes mellitus, chronic diffuse nephritis, late toxemia of pregnancy, acute edema of the lungs. The anatomic diagnosis was: chronic diffuse nephritis (arteriosclerotic with hyaline degeneration of the afferent arteries of the glomeruli); fatty degeneration of the tubules; focal sclerosis of the liver with eclamptic distribution; congestion of the viscera, ascites, hydrothorax; acute splenic tumor; involuting uterus; hydro-ureter; hydronephrosis; pyelitis, right; chronic fibrous interacinar pancreatitis. Subsidiary: hemopericardium; apical scar of the right lung; healed tubercles of the liver; lymphoid hyperplasia of the intestine.

INFANT.—Baby C., a female infant, born Sept. 23, 1924; from the menstrual history, the baby was expected about October 19. Respiration and cry were spontaneous. The child weighed 3,330 gm. and measured 48 cm. The physical examination was negative. On the third day, the child vomited portions of each feeding. It had lost 290 gm. of its weight. On the fourth day, the child had a pasty, peculiar color. The temperature that morning was 38.3 C. (100.9 F.). The baby was found dead at 7:30 p. m. The blood sugar on the third day of life was 0.067 mg. per 100 cubic centimeters of blood.

The clinical diagnosis was prematurity. The anatomic diagnosis was: hypertrophy and hyperplasia of the islands of Langerhans of the pancreas; hypertrophy of cells of medulla of suprarenal; hemorrhage and necrosis of

Fig. 3.—Photomicrograph through medulla of suprarenal showing hypertrophic cells, many of which contain hypertrophic and hyperchromatic nuclei.

suprarenals; multiple small hemorrhages into both lungs and into the submucosa of the bladder; atelectasis; bilateral double ureter and pelvis.

Necropsy.—The necropsy findings of interest were those in the pancreas and suprarenal. Besides hemorrhage, the suprarenal showed microscopically a marked increase in the size of many of the medullary cells. The nuclei and chromatin of these cells were correspondingly increased. Many of the nuclei were hyperchromatic, others vesicular. In a few nuclei the chromatin was arranged in the form of a ring. The cytoplasm in some cases was homogeneous, but many cells showed various degrees of vacuolization. A few cells were completely vacuolized. Here and there hypertrophic cells containing double nuclei were seen. Some degenerative changes were visible at various places in the suprarenal, particularly in the medulla; it is probable that these changes were largely due to autolysis

which occurred postmortem. The pancreas weighed 3 gm. and measured 4 cm. in length. It was fairly firm, slightly congested, and showed numerous small, white, pinpoint areas. Longitudinal sections were made through the whole pancreas, including the head, body and tail. The acinar tissue showed nothing unusual, but the islets were numerous and large. The cells showed no special changes, except that many of them were large and some of them very large. A few definite mitotic figures were seen. The islands were counted per 50 square millimeters and their diameters measured.

COMMENT

The figures are given in Tables 1 and 2. In Table 2 our results are compared with those of a case reported by Dubreuil and Anderodias [1]

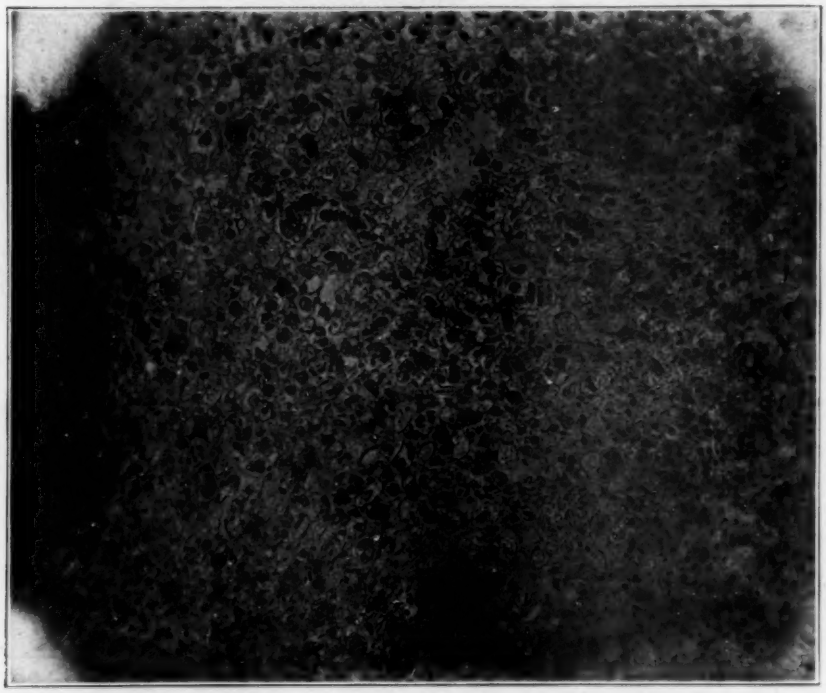

Fig. 4.—Photomicrograph of normal medulla of suprarenal of infant of same age showing the difference in size of cells and nuclei as compared with fig. 3. Same magnification as fig. 3.

This case was that of an abortion induced at the beginning of the ninth month and occurring in the course of the fourth pregnancy of a woman who had shown glycosuria in this and in a previous pregnancy at the beginning of the eighth month. The baby lived but a few minutes. It was large, weighing 5,000 gm. These authors attribute the increased weight to the large supply of sugar which was at the disposal of the child. Their only other gross finding was a large liver. Microscopically,

1. Dubreuil, G., and Anderodias: Compt. rend. Soc. de biol. **83**:1480, 1920.

they observed a marked increase in the size of the islets, but no increase in their number.

Although the total number of islands in the normal and abnormal organs was not determined, sufficient areas were counted to justify the conclusion that there was in our case a definite and marked hyperplasia of the insular tissue. Three times as many islands were found in the pancreas of this child as are found in the normal pancreas. The hypertrophy [2] of the islands was still more distinct and agrees closely with the figures given by Dubreuil and Anderodias for the case they reported, and their normal findings likewise agree with ours. The average volume of the hypertrophic insular tissue is approximately eight times that found in the normal cases. Thus, combining the hyperplasia and the hypertrophy, we have approximately a twenty-four fold increase in the quantity of islet tissue.

TABLE 1.—*Number of Islands*

Cases	Remarks	Islands per 50 Sq. Mm.
Baby C.....	Average of section from all parts of the pancreas	184
Our normal figures (6 cases)	Average of sections from infants of similar age (parts taken unknown)	64

TABLE 2.—*Comparison of Authors' Results with Those of Dubreuil and Anderodias*

Cases	Av. Diameter in Microns	Largest, Microns	Smallest, Microns	Volume in C.mm.
Average in our normal cases.....	116 × 102	206 × 198	55 × 50	0.000295
Baby C.	213 × 182	726 × 324	104 × 104	0.00236 average 0.00408 largest
Dubreuil and Anderodias, normal.....	116 × 100	147 × 120	64 × 55	
Case reported by Dubreuil and Anderodias	290 × 212	394 × 335	206 × 129	

We consider the changes found in the pancreas of this child a compensatory phenomenon. The increased sugar in the circulation of the mother on passing through the placenta into the fetal blood produced a hyperglycemia and caused an increase in insular tissue in response to the increased demand made on the island tissue of the fetus.

Joslin [3] and others [4] have noted an increased carbohydrate utilization on the part of diabetic mothers in the last month of pregnancy. In our

2. Wiener reports findings in a necropsy on a stillborn child whose mother was a severe diabetic that "some of the islands of Langerhans were larger than normal," Am. J. Obst. & Gynec. **7**:718, 1924.

3. Joslin, E. P.: The Treatment of Diabetes Mellitus, Philadelphia, Lea and Febiger, 1923, p. 652.

4. Carlson, A. J., and Drennan, F. M.: Am. J. Phys. **28**:391, 1911. Carlson, A. J.; Orr, V. S., and Jones, W. S.: J. Biol. Chem. **17**:19, 1914.

case, during the fourth month of gestation the patient was on a diet of 1,800 calories, and at the same time was taking 30 units of insulin. She was excreting 14 gm. of sugar a day. During the last or eighth month of gestation, the patient was kept sugar-free, and yet was receiving a diet of 2,235 calories and only 15 units of insulin daily. Another observation of importance which is substantiated by Wiener and is in agreement with the experimental findings of Carlson and Ginsburg,[5] is the marked rise in blood sugar following delivery. In our case, the blood sugar rose from 0.096 to 0.225 mg. per one hundred cubic centimeters of blood.

The slightly diminished blood sugar of the baby on the third day of life (0.067 mg.), with the possibility of a more marked hypoglycemia before death, is significant. The average normal is 0.09 mg.[6] It may be explained by the assumption that with the removal of the maternal sugar from the circulation of the child, the carbohydrates of the baby were utilized in an increasing amount. These facts bear strikingly on the utilization of fetal insular tissue by the mother.

Dubreuil and Anderodias do not report any increase in the number of islets. This may be due to the transient nature of the glycosuria in their patient. It developed at about the eighth month of pregnancy. Our patient, on the other hand, was diabetic practically throughout the entire period of pregnancy, and we may consider it probable that the increased amount of blood sugar in the mother acted on the pancreas of the fetus during the period of its formation and thus provided a continuous stimulus which led to the increased development of insular tissue.

The infrequency of observations such as we report in this case is attributable to two causes: (1) to the tendency toward sterility, and (2) to the practice of therapeutic abortion in the case of diabetics. Von Noorden[7] reports 5 per cent of pregnancies in 427 diabetic women who were in the child-bearing period. The obstetrical service of Barnes Hospital in a series of more than 10,000 hospital and outside cases has had five pregnancies in four diabetic women. One was delivered at term of a normal child; one had a miscarriage at eight months; two pregnancies were therapeutically terminated in the third month; the fifth case is that reported above. During this period 205 women of child-bearing age have been treated for diabetes mellitus in Barnes Hospital.

The interpretation of the hypertrophy of the medullary cells of the suprarenal which we observed is difficult. Of twenty suprarenals of the new-born which we examined, only one showed some hypertrophy, but

5. Carlson, A. J., and Ginsburg, H.: Am. J. Phys. **36**:217, 1915.
6. Joslin, E. P.: Am. J. Phys. **36**:656, 1915.
7. Von Noorden, C., quoted by Wiener: Am. J. Obst. & Gynec. **7**:718, 1924.

neither the size nor the number of cells approached those observed in this case. Perhaps the supposed antagonistic action between the suprarenal and pancreas offers an explanation of our findings, the hyperactivity of the islands calling forth an increased activity and consequently an hypertrophy of the medullary cells. However, only further observations in similar cases can decide the latter question.

SUMMARY

A case is reported in which the pancreas of a child born of a diabetic mother contained approximately twenty-four times as much insular tissue as the normal pancreas.

The increase in maternal blood sugar is suggested as the stimulus which called forth the increase in insular tissue in the pancreas of the child.

Hypoglycemia, the result of this insular hypertrophy and hyperplasia, may play a rôle in the sudden death of the baby.

Associated with the hypertrophy of the islands of Langerhans was an hypertrophy of many medullary cells of the suprarenals.

THROMBOPENIC PURPURA *

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AND
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In the mysterious group of splenic diseases, one clinicopathologic entity has been set apart during recent years. Thrombopenic purpura or essential thrombopenia affects women particularly (80 per cent. of cases), and it may be of acute or chronic course. The most prominent clinical feature is "bleeding from everywhere," causing marked anemia and frequently death. The diagnosis is made on the basis of low platelet count, sometimes even below 15,000 instead of the normal 250,000 to 350,000 per cubic millimeter, normal coagulation time (in contrast to hemophilia and allied conditions) with no retraction of blood clot and hence prolonged bleeding time. A tourniquet on an extremity produces petechiae in the distal part in five minutes. The spleen is sometimes enlarged but in other cases normal.

Kaznelson [1] was the first to perform splenectomy in a case of this kind. The results were so encouraging that by the end of 1924 about forty instances of operation in thrombopenic purpura were reported, and this number probably has been doubled during the last year (Giffin,[2] Beth,[3] Rosenthal,[4] Leschke,[5] Höglund,[6] Harttung,[7] Engel,[8] Nagy,[9] Dyke [10] and many others).

In our case we have a rather uncommon example of the beneficial influence of splenectomy on extremely severe acute essential thrombopenia. According to Harttung,[7] in twenty chronic cases twelve patients were cured by splenectomy, while in five acute cases three died.

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* From the West Suburban Hospital.

1. Kanzelson: Wien. Arch. f. inn. Med. **7**:87-116, 1923.

2. Giffin, H.: M. Clinics N. America **8**:1153, 1925.

3. Beth: Boston M. & S. J. **193**:191, 1925.

4. Rosenthal, N.: Clinical and Hematologic Studies on Banti's Disease; Blood Platelet Factor with Reference to Splenectomy, J. A. M. A. **84**:1887 (June 20) 1925.

5. Leschke, E.: Deutsch. med. Wchnschr. **51**:1352, 1925.

6. Höglund: Acta med. Scandinav. **62**:197-377, 1925.

7. Harttung: Deutsch. Ztschr. f. Chir. **191**:91, 1925.

8. Engel: Arch. f. klin. Chir. **129**:563, 1924

9. Von Nagy, G.: Thrombopenia and Essential Thrombopenia, Ztschr. f. klin. Med. **100**:630, 1924.

10. Dyke: Lancet **2**:715, 1924.

REPORT OF CASE

History.—A white woman, aged 25, unmarried, the patient of Dr. L. F. Alrutz, was admitted to the hospital on Feb. 13, 1925, complaining of bleeding from the genitalia, nose, mouth and gums, and also of bloody spots under the skin.

The condition had started five days before. The usual menstrual period being almost over, profuse flow suddenly began again and continued freely, with clots at times. A few hours after the flow started, she began to bleed from the mouth and gums; the next day she noticed also ecchymoses on the left thigh and later on the left shoulder, right thigh and both feet. She also had vomited blood. The first three days after the bleeding started she had headache and was thirsty. Her past history was negative. Her parents, sister and two brothers were living and well.

Physical Examination.—The patient was in rather poor condition. She was pale, with blood on the lips and large ecchymotic spots all over the body. The mucosa of the mouth was hemorrhagic and bleeding. One carious tooth was present. The nasal cavity contained blood. There were numerous hemorrhagic spots over the chest, abdomen and arms; there was a large green-black ecchymosis on the right shoulder. There were large ecchymoses on each thigh and a few smaller ones on each leg and numerous bright red petechiae below each knee. The sphygmomanometer applied to the arm at 100 mm. of mercury produced petechiae in five minutes.

Results of Blood Tests

	Feb. 11.	Feb. 13.	Feb. 17. Splenectomy.	Feb. 27.	July 1.
Erythrocytes	3,060,000	2,580,000	1,780,000	2,320,000	4,070,000
Hemoglobin	65%	55%	38%	....	83%
Leukocytes	7,250	7,700	.....	9,280	8,700
Polymorphonuclears	71%	....	....	....	57%
Small lymphocytes	16%	....	....	....	36%
Large lymphocytes	13%	....	....	....	7%
Platelets	.....	15,000	430,000*	470,000	210,000

* Eighteen hours after operation.

The blood tests, and especially the low platelet count, confirmed the diagnosis of essential thrombopenia.

The coagulation time was three and one-half minutes. There was no contraction of the blood clot; the bleeding time was sixty-five minutes. The urine contained numerous red and white blood cells.

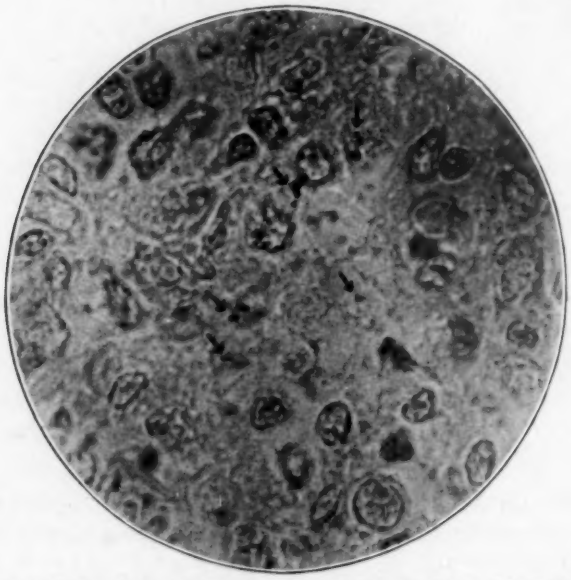
In spite of repeated blood transfusions and abundant vitamine supply, the patient became progressively worse. February 17, Dr. J. L. Nortell performed splenectomy, followed by transfusion of 750 c.c. of citrated blood. The bleeding ceased almost immediately after the operation. The platelets rose above the normal level a few hours later. The patient made an uneventful recovery and left the hospital two weeks after the operation. She has been in perfect health.

Examination of the Spleen (E. C. Piette).—The spleen measured 10 by 6 by 3.5 cm. and weighed 110 gm. The capsule was smooth; the cut surface was deep purple, and a thin grayish network of trabeculae was slightly visible. The malpighian corpuscles were slightly prominent by side light. The pulp was rather firm, and did not project from the cut surface.

The cultures of the splenic juice made immediately after operation on plain agar, blood agar and dextrose broth remained sterile. Several pieces of spleen were fixed in Bouin's fluid and embedded in paraffin; serial sections 4 microns thick were stained with hematoxylin-eosin, Gram-Weigert and methylene-azur eosin, and frozen sections were stained with ferrocyanide of potassium for iron.

Microscopically, under low power magnification, the general structure of the spleen seemed to be normal; only the glomeruli were decidedly decreased in size and number. The venous sinuses were not dilated. In one place near the lower pole a focus of subcapsular hemorrhagic infiltration was seen, evidently being due to operative trauma, for no similar changes were seen in other places.

Marked fibrosis of the reticular tissue was visible in the red pulp as well as in the center of the glomeruli. Mitoses in reticulo-endothelial cells were rather numerous, about one to three in each high power field. In the red pulp many neutrophilic and eosinophilic myelocytes were present. No bacteria were found.



Partly digested platelets within the cytoplasm of splenic reticular and endothelial cells. Section of spleen, fixed in Bouin's fluid, methylene-azur-eosin. Magnification, 1200 diameters; oil immersion.

As to the amount of iron containing pigment, it seemed to be rather decreased, being present only about the vessels.

The most interesting findings were discovered by the oil immersion. Within the cytoplasm of the endothelial cells of venous sinuses and also in the reticular cells of the glomeruli, numerous small irregular granules were found. They were stained deep blue with methylene-azur and were practically invisible in hematoxylin-eosin sections. These granules were, in our opinion, degenerated blood platelets normally present in the spleen in much less numbers. Some better preserved platelets were also seen in the cytoplasm of endothelial cells. The picture of enormously increased phagocytosis of the platelets by the reticulo-endothelial cells of the spleen may help to explain the decrease of platelets in the blood stream and the associated hemorrhagic diathesis and also the effect of splenectomy and subsequent rapid increase of platelets.

COMMENT

Two theories are in vogue to explain the pathogenesis of thrombopenic purpura. Frank [11] believes the condition to be due to primary deficiency of the bone marrow, in other words, to a decreased production of blood platelets. On the other hand, Kaznelson [1] and most of the other authors interpret this disease as increased destruction of blood platelets by splenic cells. Cory [12] found by direct count in a case of essential thrombopenia that the platelets in the splenic vein are much less in number as compared with those in the splenic artery. The bone marrow, according to Kaznelson,[1] Sternberg and others, shows no changes in thrombopenia, and the number of megakaryocytes (which are believed to produce platelets by separation of their cytoplasm) is within the normal limits.

In the recent work of Seelinger, many important facts are established. Examining bone marrow obtained by sternal puncture from patients with thrombopenia, he divides them into two classes:

Cases of "essential thrombopenia" with a normal or increased number of megakaryocytes. Here the spleen is packed with abnormal platelets, and good results are obtained after splenectomy. Cases of "aleukia" with aplastic marrow, showing few hematopoietic cells of any kind. There is a decrease not only in platelets but also in white cells. Splenectomy has no effect.

Megakaryocytes in thrombopenic purpura in his opinion are mostly abnormal, containing few granules in their cytoplasm, and hence are incapable of producing normal platelets. In his opinion the cause of thrombopenia is toxic damage, lowering the function of megakaryocytes. His results well deserve further study.

Unfortunately, we have no means of removing the whole reticuloendothelial system from the body; numerous elements of the same nature are present in the liver, lymph nodes, bone marrow, etc. Therefore the danger of relapse of hemorrhagic diathesis is not excluded by splenectomy, as is shown by cases of Foerster [13] and Sternberg,[14] in which relapses with fatal termination took place after splenectomy. Bedson [15] showed that in normal guinea-pigs splenectomy is followed by a great but temporary rise in the number of platelets, manifested in forty-eight hours, reaching a maximum in from ten to fourteen days and subsiding to normal level in three or four weeks. As a rule, however, patients remain free from symptoms in some cases even as long

11. Frank: Berl. klin. Wchnschr., June 11, 1917, p. 573.
12. Cory, G.: Ztschr. f. klin. Med. **94**, 1922.
13. Foerster: Ztschr. f. klin. Med. **92**:170, 1921.
14. Sternberg: Wien. Arch. f. inn. Med. **3**:433 (Jan. 20) 1922.
15. Bedson: Lancet **2**:1117 (Nov. 29) 1924.

as seven years after operation. These beneficial results could be explained on the basis of Seelinger's [16] findings. He states that neither the Kupffer cells of the liver nor the reticulum of the lymph nodes and bone marrow contain any traces of blood platelets. The opinion is therefore justified that the involvement of the reticulo-endothelial system in thrombopenic purpura is limited to the spleen.

Thus from a histologic standpoint, splenectomy, a natural measure in traumas or in isolated infection of the spleen, is justified only in two "essential" conditions: in hemolytic jaundice, in which enormous quantities of erythrocytes are destroyed by the reticulo-endothelial cells of the spleen, and in thrombopenic purpura, in which the blood platelets are undergoing the same kind of destruction.

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16. Seelinger: Klin. Wchnschr. **3**:731 (April 22) 1924.

GOUNDOU IN A MONKEY

REPORT OF A CASE

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The name goundou, big nose, is given to a condition of unknown etiology, characterized by symmetric, hard, smooth, painless swellings (bony exostosis) at the sides of the nose; the swellings have an oval form, with the long axis downward and slightly from within outward. The disease, which occurs in Central Africa, Sumatra, China, South America, the West Indies, etc., affects not only man, but also some species of monkeys.[1]

The first cases of goundou, also named "henpuye," dog nose, or "anákhré," big nose, were reported in 1882 by MacAllister under the term "The Horned Men of Africa." Lamprey, in 1887, described the disease with drawings. In 1924, Strachan described a case in a child in the West Indies, and in 1895 Maclaud [1] related that cases are relatively frequent in the region of the Niger River, the disease being called "goundou" or "anákhré."

It has now been found that goundou is spread throughout all tropical countries, that it affects not only negroes, but also other races, including the white, and that a similar condition is encountered in monkeys. It seems that even the ancient Incas were affected with goundou, as Letulle found the condition in one of their skulls in a Peru necropolis.

Recent observations suggest that the bone formations may not be limited to the superior maxilla, but may affect other bones as well.

The etiology of the disease remains unknown. Botreau-Roussel (quoted by Joyeux [1]) urges that goundou is a sequel of yaws, a belief prevalent among the inhabitants of Oubangui and the tribe of Gourea (Ivory Coast), who give the name of "dougou" to both yaws and goundou. This view, however, is not in harmony with the fact that in some countries in which yaws exists, goundou does not, as at Laos, for instance; that monkeys may suffer from goundou, while up to the present no cases of yaws have been found in these animals; and that occasionally patients with yaws may have a unilateral or bilateral swelling of the nose

1. Castellani and Chalmers: Manual of Tropical Medicine, London, Bailliere, Tindall and Cox, 1919, p. 1975. Manson-Bahr: Tropical Diseases, ed. 7, New York, William Wood & Company, 1924, p. 741. Joyeux, C.: Goundou, in Roger, H.; Widal, F., and Teissier, P. J.: Traité de médecine (nouveau), Paris, Masson & Cie, **1**:55, 1924.

(pseudogoundou of Brumpt), but if the patient is treated with potassium iodide or arsphenamine, the swellings disappear with the recovery from the yaws, while the swellings of goundou do not suffer any modifications from such treatment. Other authors, according to Castellani and Chalmers,[1] have advanced the opinion that goundou is caused by larvae of flies, but there is no proof in favor of this view.

The reports of cases of goundou indicate that the disease begins with an acute mucopurulent nasal discharge followed later by the bony swellings. The disease usually begins in childhood with headache and a mucopurulent discharge (at times accompanied with blood) from the nose. After several months the discharge ceases, and two swellings, one on each side of the nose (rarely unilateral), corresponding to the nasal processes of the superior maxilla, start to develop.

It is the second period of the disease, the period of bony swellings, that has been studied both in man and in monkeys. It is agreed that the two swellings are bony outgrowths from the nasal process of the superior maxilla, sometimes affecting the maxilla itself. These swellings grow slowly, are painless, and have the consistency of bone. The skin over them is movable.

The swellings grow continuously, and may reach an enormous size, interfering with vision and sometimes causing blindness. When well developed, the swellings are oval, with the maximum diameter directly downward and outward from the nose. The growths do not recur after removal. The nasal mucosa may be normal, but some authors describe polypoid excrescences in the mucosa which occasionally may close the nasal cavity. According to Botreau-Roussel, who examined 150 patients with goundou, the disease not only affects the nose, but also other parts, especially the tibia, but as he considers goundou as a secondary manifestation of yaws, he therefore may have mistaken the lesions of this disease for those of goundou.

Almost all authors agree that the characteristic outgrowths from the nasal process of the superior maxilla are of an inflammatory nature. They are formed of spongy bone. Starting from the opinion that the disease has its beginning in the nasal cavity, the hypothesis has been advanced that the unknown virus is carried from the nasal cavity by means of the blood through the blood vessels of the "sutura notha" to the nasal process of the superior maxilla, where it determines the bony outgrowths.

The following case in a monkey may be of interest:

REPORT OF CASE

A monkey, *Cynocephalus sphinx*, weighing 4,500 Gm., was received in perfect health in November, 1922, at the University of North Dakota. On November 20, there were 30,000 leukocytes per cubic millimeter, 65 per cent of which were

lymphocytes. On June 15, 1923, there were 24,000 per cubic millimeters, 49 per cent of which were lymphocytes.

On December 15, in the morning, the animal, heretofore always well, appeared sick. During the previous night, the window of the laboratory had been left open, and the temperature of the room had dropped to 5 or 6 below zero; ordinarily the temperature had been 16 to 18 degrees above. On this day, a severe cold, with a profuse flow of mucus from the nose, developed. The monkey was kept warm, and placed on a milk diet.

On December 16, the condition was worse, the cold having become complicated with a catarrhal bronchitis.

On December 18, the bronchial condition improved; abundant mucopurulent whitish yellow discharge flowed from the nose; the appetite was good.

The discharge continued to flow abundantly from the nose, but toward the end of January, 1924, it diminished, and at the end of March the animal appeared well, with almost no discharge. Unfortunately, the discharge was not examined bacteriologically.

Cynocephalus sphinx seventeen months after disease had started.

On May 15, it was noticed that on each side of the nose there was a symmetrical swelling, about the size of a bean, 1.5 cm. long and 0.5 cm. wide. The swellings had an oval shape, with the long axis downward and slightly outward. They felt hard as bone, and seemed painless to the animal; the skin over the growths was soft and freely movable. The mucosa of the nose was dry, with no discharge.

On October 1, the animal was in good health; but the hard, smooth, bony masses at the sides of the nose had increased noticeably in size. The nostrils bulged inwardly somewhat, and the animal had difficulty in breathing through the nose.

On Jan. 6 1925, the animal seemed normal, with the exception of the swellings at the sides of the nose; the disturbance in breathing through the nose was not increased. An examination of the blood gave: red blood cells, 5,250,000; white blood cells, 6,000; hemoglobin, 88 per cent.

The leukocytic formula was: small lymphocytes, 3 per cent; large lymphocytes, 16 per cent; transitional forms, 30 per cent; large mononuclears, 16 per cent.

Polymorphonuclear cells: neutrophils, 26 per cent; basophils, 2 per cent; eosinophils, 2 per cent.

On June 25, the animal was in perfect health, but the two outgrowths had increased so that its vision was impaired; the nose had become much deformed. The animal was killed by ether anesthesia.

At necropsy, all the organs appeared normal; the face showed the two swellings at the sides of the nose. Each swelling arose from the anterolateral surface of the superior maxilla, of which a great part of the "corpus" and the "frontal process" were involved. The nasal cavity showed no polypoid excrescences, but was deformed and diminished in size. One of these swellings (the right one) was removed; the skin over the outgrowth showed no lesions. The swelling was composed of a thin shell of compact bone, beneath a spongy tissue, easily cut. Small pieces of the bone were fixed in 8 per cent formalin, and then passed into Müller's fluid; after several days, a green, deeply stained zone about 1 cm. deep at the periphery, could be seen, marking recent bone formation.

Sections of decalcified pieces were stained with hematoxylin-eosin and alum-carmin. Microscopically, the outgrowth appeared to be composed of osseous and osteoid tissue and connective tissue in different stages of development; there was abundant vascularization, and in some parts red marrow with fat cells. The osseous and osteoid tissue were surrounded by osteoblasts, which indicated an active bone formation; there were few osteoclasts; the new haversian canals showed an irregular lamellar system; the connective tissue consisted in a great part of fibroblasts in bundles, limiting numerous blood spaces which had only a simple layer of endothelium as a wall. In many points the vascularization was so great that the tissue took on an angiomatous appearance. In relatively few parts, the connective tissue was fibroid, with but few blood vessels.

The swellings, then, were due to abnormal bone formation, still in active growth, on an inflammatory basis.

SUMMARY

The monkey first suffered with marked mucopurulent inflammation of the nasal cavity, which lasted for more than three months, and toward the end, outgrowths appeared on the superior maxilla at each side of the nose. These two swellings continued to grow, with no indication of arrest, until the animal was killed.

The facts that the animal was stricken in youth and that the characteristic maxillary outgrowths were preceded by a mucopurulent rhinitis, warrant the diagnosis of the malady as goundou.

FOUR UNUSUAL MALIGNANT TUMORS OF THE LIVER*

WITH FOUR PLATES

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In reviewing the older literature of liver tumors, one is struck by the paucity of references to any but the usual metastatic tumors. During the past few years, however, there has been an increased interest in primary carcinomas of the liver, of both the liver cell and bile duct epithelial types. An article by Fried,[1] last year, reviews the current bibliography and reports five cases, four of which were of the bile duct variety and one of the liver cell type. It has long been my intention to report twelve cases of primary carcinoma of the liver, which it was my good fortune to observe during the course of a year's stay in the Philippine Islands. Interestingly enough, and by way of contrast to the series which Fried reported, the opposite was true in that nine of these twelve were of the primary liver cell type, while only three were of the typical bile duct epithelial type. The ages of the patients ranged from 10 to 64 years.

In the Orient, especially in the more tropical portions, it seems to be generally accepted by clinicians that primary carcinoma of the liver is a definite disease entity and one which can readily be recognized. Unfortunately, symptoms rarely develop until a comparatively short time before death, the course of the disease after the symptomatic onset averaging rather less than four months, in some instances only three or four weeks. Enlargement of the abdomen, owing to the progressive enlargement of the liver, is usually the first clinical finding noted. This is followed by ascites, pressure symptoms relating especially to the gastrointestinal tract and the cardiorespiratory system. Terminally, there is usually jaundice. In a few cases the jaundice is the first symptom observed by the patient.

Clinically, it is generally recognized that there is usually a cirrhosis of the liver associated with the development of the carcinoma, the cirrhosis, as far as known, invariably preceding the tumor formation and commonly being conceded as being due to chronic infections of intestinal origin, either bacterial or parasitic. This is borne out by Ewing's state-

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1. Fried, B. M.: Primary Carcinoma of the Liver, Am. J. Med. Sc. **168**: 241, 1924.

ment that 85 per cent. of the cases of hepatoma and 50 per cent. of the biliary type are associated with cirrhosis.

Statistics of the incidence of primary carcinoma of the liver seem to suggest that less than 0.5 per cent. of all deaths from carcinoma are of this variety. The figures unfortunately are difficult of analysis, as they are incomplete in many instances. We find that Bokay and Goldzieher [2] reviewed 6,000 necropsies at the Pathological Institute of Budapest and found only eighteen cases of primary carcinoma of the liver (an incidence of 0.3 per cent.). Hale White [3] found only ten cases in 10,000 necropsies at Guy's Hospital (an incidence of 0.1 per cent.). Winternitz [4] found only three cases in a series of 3,700 necropsies (an incidence of 0.08 per cent.). Clawson and Cabot,[5] from Minnesota, reported one case in 5,100 necropsies (an incidence of 0.019 per cent.). Von Glahn and Lamb [6] found six cases in a consecutive series of 1,800 necropsies at the Presbyterian Hospital (an incidence of 0.33 per cent.). Castle,[7] in reviewing the literature from 1841 to 1913, found forty-two cases in children under sixteen. In Fried's series of four cases among 1,200 necropsies, we find the relatively high figure of 0.33 per cent. The twelve cases which I take the opportunity to record occurred in a series of 872 necropsies, of which somewhat less than seventy were cases of malignancy.

Incidentally, it is of passing interest to state that during the interval fully as many patients went home from the Philippine General Hospital with the clinical diagnosis of malignant disease of the liver as came to necropsy, and there seems to be no reason to doubt the clinical diagnosis as all the cases coming to necropsy were recognized antemortem. This suggests an extraordinarily high incidence of this particular form of carcinoma in this part of the world, as this disease causes 1.3 per cent. of the total number of deaths in this series and about 17 per cent. of the deaths associated with malignancy. In view of the rather voluminous literature on this particular type of tumor, it does not seem worth while recording in detail the individual protocols. One case which

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2. Bokay and Goldzieher: Das primäre Leberkrebs, Virchows Arch. f. path. Anat. **203**:75, 1911.

3. White, Hale: A Case of Primary Melanotic Carcinoma of the Liver, Tr. Path. Soc. London, 1886, p. 272.

4. Winternitz, M. C.: Primary Carcinoma of Liver, Bull. Johns Hopkins Hospital **73**:165, 1912.

5. Clawson, B. J., and Cabot, V. S.: Primary Carcinoma of the Liver, J. A. M. A. **80**:909 (March 31) 1923.

6. Von Glahn, W. C., and Lamb, A. R.: Primary Carcinoma of the Liver, M. Clinics N. America **8**:29, 1924.

7. Castle, O. L.: Primary Carcinoma of the Liver in Childhood, Surg., Gynec. & Obst. **18**:477, 1914.

occurred in an unusually young person will serve to illustrate. The others are all of the same nodular variety associated with a diffuse cirrhosis. This represents the commonest of the three generally recognized types: the massive, the diffuse and the nodular.

REPORT OF CASES

History.—A Filipina, aged 10 years, was admitted to the Philippine General Hospital, service of Dr. José Albert, with a clinical history of about two months' duration. During this time there had been slow but progressive increase in the size of the abdomen, accompanied by increasing dyspnea and general abdominal discomfort.

Physical Examination.—The patient was a fairly well developed and well nourished Philippine girl. The outstanding finding was the prominent abdomen. This was due in part to an increase in the size of the liver, but chiefly to the presence of a marked ascites. Examination of the heart and lungs showed them to be within normal limits. The spleen was ballotable and obviously enlarged, although its outlines could not readily be made out. There was marked jaundice of the sclerae, mucous membranes and skin. No petechiae were seen.

Clinical Notes.—The patient was in the hospital only a week and grew steadily worse. She was tapped twice, but with only temporary relief. The laboratory findings were negative.

Necropsy.—The body was that of a fairly well developed but somewhat emaciated girl of about 12 years of age in appearance. There was a marked icteric discoloration of the sclerae, mucous membranes and skin. The facies otherwise were not remarkable. There were a few small palpable cervical lymph nodes. There was marked prominence of the abdomen, and two midline scars were noted between the umbilicus and symphysis, apparently representing intraperitoneal paracenteses. There was still a large amount of fluid in the abdominal cavity and a definite fluid wave could be obtained. The abdomen was asymmetrical, owing to marked enlargement of the liver, which could be percussed to the level of the iliac crest, and extending diagonally to the left anterior axillary line. The spleen could also be outlined just beneath the liver margin.

The primary incision extended from the sternum to the symphysis pubes. The pleural cavities and the pericardial cavity contained no free fluid and no adhesions. The heart was essentially normal. The lungs were moderately congested and edematous at the bases. There were definite areas of fibrous tissue thickening at the right apex and some enlargement of the mediastinal lymph nodes, but no evidence of active tuberculosis was noted. The chief pathologic condition was found in the abdominal cavity. The peritoneal surface was smooth and glistening. About 5 liters of clear straw-colored fluid were removed from the peritoneal cavity; this contained a few flecks of fibrin. The spleen was moderately pigmented, suggesting an old malarial infection. There was some fibrosis of its capsule. The stomach was normal. The duodenum was moderately injected and showed a catarrhal inflammatory reaction of the mucosa. The ileum was negative. There were, however, about a dozen adult ascaris worms in the small intestine. The cecum contained several dozens of adherent *Trichocephalus trichiura.* The colon was normal. The pancreas was normal. The kidneys were somewhat pale and edematous. Their capsules stripped readily. No particular pathology was noted. The suprarenals were negative.

The chief pathologic condition of the liver was a massive nodular tumor, the right lobe being the more completely involved. The liver weighed 4,500 gm. It was pale, except for irregular areas of bile staining, which represented the persistent liver parenchyma. Its surface was irregularly nodular, but no extension of the tumor through the capsule was noted. The gallbladder appeared somewhat thickened, but not involved in the tumor formation. On section the most striking feature of the pathology was the extensive infiltration of the venous channels by tumor tissue, practically obliterating the hepatic veins. In many places the tumor tissue was firmly adherent to the vessel wall, acting apparently as a thrombus. In other areas it could be detached, and apparently had propagated from some initial focus without actually involving the intima. Numerous areas of necrosis and hemorrhage were found. There was no evidence of metastasis, except into a few regional lymph nodes which were intimately bound to the liver tissue.

Microscopic Examination.—The entire histologic interest centered in the liver tumor, which was of the typical liver cell type of adenocarcinoma. It was composed of massive sheets of liver cells, in places tending to form trabeculae and even forming atypical appearing bile canaliculae, with a stroma consisting of a few strands of connective tissue and vascular sinuses comparable to the normal liver sinusoids. Looking at the tumor tissue without comparison with the persistent liver cells, it might be difficult to say whether one were dealing with a tumor or with an atypical regeneration, except for the absence of portal areas, the relative frequency of mitotic figures and the irregular size of many of the cells. However, in areas in which the tumor encroached on the normal liver trabeculae, the differentiation was apparent, as the tumor cells were more basophilic in their staining reaction, the cytoplasm of the individual cells was relatively much increased as compared to the normal, and a much less orderly arrangement of the trabeculae occurred than was noted in the normal liver tissue. The bile staining of the remaining liver parenchyma was likewise absent in the tumor tissue. The microscopic diagnosis was primary carcinoma (hepatoma) of the liver (Plate I, Fig. 1).

Comment.—There is no difficulty in the diagnosis of this type of liver cell tumor. The chief interest lies in considering the etiology, especially in relation to the geographic distribution and relative infrequency as compared to other carcinomas. In the series of 872 necropsies cited, only one case of primary carcinoma of the head of the pancreas was found. This is in direct contrast to the usual findings in the literature of the accident. It creates a paradox, for there should be a corresponding increase in pancreatic carcinoma, if chronic inflammation plays a part, for the pancreatic duct is nearly as liable to bacterial or parasitic invasion as is the bile duct.

Yamagiwa,[8] Pirie[9] and Forsyth[10] all emphasize the relationship of cirrhosis to the multicentric development of the tumor. Pirie especially

8. Yamagiwa: Zur Kenntniss der primären parenchymatosen Leberkarzinom (Hepatoma), Virchows Arch. f. path. Anat. **206**:437, 1911.

9. Pirie: Hepatic Carcinoma in Natives of Africa and Its Frequent Association Schistosomiasis, M. J. South Africa **17**:87, 1921.

10. Forsyth, W. L.: Primary Carcinoma of the Liver, Indian M. Gaz. **57**: 295, 1922.

comments on the frequency of schistosomiasis as a cause of the cirrhosis in certain West African tribes, and reports thirty-six cases of primary liver carcinoma among a total of ninety-six cases of carcinoma which he had seen over a period of nine years. Twenty-eight of his cases were of the liver cell type. Ten of these were proved to have an associated schistosomiasis, and in only two of the remainder could it be ruled out.

Other views are expressed as regards the concurrence of cirrhosis and carcinoma. Many cases of carcinoma without cirrhosis (Rolleston) have been reported. In this part of the country among the thousands of cases of cirrhosis, how rare it is to find primary carcinoma! Obviously, therefore, these conditions can occur independently.

It is possible that the two may occur coincidentally and without any causal relationship. On the other hand, Pirie feels strongly in relation to schistosomiasis that it is not only the ova which act as a mechanical irritation, but also that the parasite exerts a toxic effect as well which stimulates the cirrhosis and probably the development of carcinoma. Winternitz also comments on the possibility of a single agent acting in producing both cirrhosis and carcinoma.

Another point which merits attention is the question of the unicentric or multicentric origin of these tumors. In this particular case it seems to me more likely to have been multicentric, although the arguments of the blood vessel involvement and the distant metastases have been used repeatedly to emphasize a unicentric origin. The tumor nodules in this case seem too uniform in appearance and too widespread in distribution to have arisen from a single focus. No doubt in individual cases either or both origins may be true. This seems to be principally a point of academic rather than practical interest.

The second case is incomplete, both in its clinical and pathologic aspects, but it is included because of its comparative infrequency.

Case 2.—We have no detailed history of the case of Mrs. Elizabeth P., aged 50, but it presents some interesting pathologic features. The material was removed operatively. At the time of operation several tumor nodules adherent to the wall of the intestine were noted and similar nodules were seen in the liver. Several of these were excised and sent in for histologic examination. They were small, irregularly spherical masses, not over 1 cm. in diameter, pearly white and rather dense. They appeared indefinitely encapsulated by the liver tissue. On microscopic examination the histology was shown to be that of a metastatic leiomyosarcoma, presumably of gastro-intestinal origin. No subsequent data on the case have been obtained, so that the etiology of the tumor still remains somewhat in question, as it might as easily have been primary in the uterus.

Comment.—Goldstein,[11] in the *Medical Clinics of North America,* in a study of the literature over a period of nearly fifty years, remarks

11. Goldstein, H. I.: Primary Sarcoma of the Liver with Report of a Case, Internat. Clin. **2**:73, 1921.

that of the 592 reported cases of sarcoma of the gastro-intestinal tract and adnexa, 265 were primary in the stomach, 130 in either the large or small intestine, and that in only 59 was the liver involved. This suggests the relative infrequency with which such tumors are encountered.

CASE 3.—*History.*—A woman, aged 68, with an essentially negative family and marital history except for sterility during the twenty-four years of her married life, was admitted to the service of Dr. H. M. Clute. Her past history was of little significance. Her weight had been constant for the past four years. The menopause occurred at the age of 55.

About ten weeks before admission, the patient noted that her abdomen appeared somewhat swollen. This condition was accompanied by occasional vomiting. Since that time there had been intermittent attacks of vomiting without pain. About a week before admission, she suffered from a lower abdominal pain of a rather diffuse character. The abdomen slowly but steadily increased in size. The chief complaint was a progressive weakness, so that for more than a week before entrance she was unable to get up to attend to her ordinary household duties.

Physical Examination.—The heart was normal. The lungs showed slight edema at the bases, with a few crackling râles. The abdomen was diffusely distended. No fluid wave could be detected definitely. It was thought that a mass could be felt in the left upper quadrant, and cystoscopy was advised.

Laboratory Data.—Cystoscopy and pyelograms were negative. A roentgenogram of the abdomen was unsatisfactory. The renal function was 31 per cent. The nonprotein nitrogen was normal, 26.7 mg. per one hundred cubic centimeters. The icterus index was 39.

Operation and Course.—A preoperative diagnosis of probable ovarian cyst or ascites was made. Through a small incision of the abdominal wall a large amount of clear serous fluid was removed. The liver was palpated and found to be contracted and nodular, suggesting the characteristic findings of a late stage of atrophic cirrhosis. No other pathologic condition was found.

The patient improved slowly for about a week, and then began to develop a progressive jaundice, which became marked before death. She gradually grew weaker, occasionally vomiting, and during the last forty-eight hours became semicomatose.

Subsequent Notes.—In view of the pathologic findings at necropsy, a careful inquiry into the past history was made, with especial reference to eye symptoms, but nothing of significance was discovered. Unfortunately, necropsy was restricted, so that the head could not be examined.

Necropsy.—The body was that of a well developed and somewhat obese woman 67 years old. There was a definite icteric tinge to the entire skin as well as to the mucosae and sclerae. The pupils were regular and equal, measuring 3 mm. each. No external lesions were noted, except the scar of an abdominal incision, which was 12 cm. in length and was located just below the umbilicus in the midline. This had practically healed. There was moderate distention of the abdomen by fluid which could be felt through the abdominal wall.

The primary incision was made from the tip of the xyphoid to the symphysis. About 2 liters of clear straw-colored fluid were removed from the abdominal cavity. Nothing of an abnormal character was otherwise noted except the liver. The appendix was retrocecal in position and firmly bound down by

adhesions. There was a moderate amount of fat in the omentum and mesenteries. There was no definite enlargement of the mesenteric lymph nodes. The diaphragm reached the fifth rib on the right and the fifth interspace on the left.

The liver weighed 1,680 gm. Its capsule showed some thickening here and there, and a few places showed local accumulations of small amounts of fat apparently under the capsule. The most striking feature of the liver was its extraordinary color, which was a mottled yellowish-greenish black resembling granite. The cut section of the liver presented the same mottled granite surface with some suggestion of bile staining of the tissues. Throughout the liver there were areas of black or gray which resembled the anthracosis usually seen in the lungs and mediastinal lymph nodes. There was extreme cirrhosis of the liver. It was resilient on section and cut with markedly increased resistance. The anatomic relations of the lobules were not readily made out, which was confirmatory evidence of the atrophic type of cirrhosis. Were it not for the color, it would resemble the liver of hemochromatosis. There were a few small areas from 1 to 3 mm. in diameter, which were grayish white and represented areas of fibrosis. The gallbladder and ducts were essentially negative. There was some dilatation of the common duct with subsequent distention of the gallbladder, but no stones were found and no definite evidence suggesting inflammatory choledochitis. The retroperitoneal lymph nodes, which were enlarged to almond size, in the region of the bile ducts, showed similar pigmented changes.

The pancreas was somewhat enlarged, particularly its duodenal portion. This was due in part to fatty infiltration and fibrosis and in part to what appeared to be a hyperplasia associated with an inflammatory process. There were a number of small greenish-yellow foci resembling caseous material, which could be expressed from what were presumably either dilated ducts or acini. Surrounding some of these areas were foci of fat necrosis and fibrosis.

The spleen weighed 270 gm. It showed moderate enlargement and gave the impression of some increase in connective tissue as it cut with considerable resistence. The malpighian corpuscles were not prominent, although they could be made out. The increase in size seemed to be due to connective tissue rather than lymphoid hyperplasia.

The right kidney weighed 120 gm.; the left, 175 gm. Their capsules stripped readily, leaving a smooth surface. The normal ratio of cortex and medulla was present. The right kidney showed no gross evidence of a pathologic condition. The left kidney showed several rather deep scars on the surface, presumably representing vascular lesions. In addition, there was a definite hemorrhagic pyelitis involving most of the pelves and the calices of the superior pole. The ureters and bladder were normal.

The suprarenals were normal in size, color, consistency and position. They showed no change except moderate postmortem degeneration. The lungs and heart were examined through the diaphragm, and with the exception of a few old calcified nodules on the pleural surface near the apexes, no gross pathologic changes were noted. The heart apparently was contracted normally in systole. It was not increased in size.

The stomach was distended moderately but showed no gross changes. There were no pathologic lesions of significance throughout the entire length of the gastro-intestinal tract.

The uterus was very small, almost infantile in type. Both ovaries were atrophic and showed no evidence even of follicular degeneration. They were firm and fibrosed in consistency.

Microscopic Examination.—Histologically there were two outstanding lesions in the liver; a diffuse cirrhosis and a pigmented tumor. The cirrhosis appeared not to be definitely related to the presence of the tumor, and apparently antedated it by a considerable period of time. It was not typical, however, of either the common atrophic (Laennec's) type or of the usual infectious biliary type. It suggested rather the less common diffuse hypertrophic (Hanot's) type for which no satisfactory explanation has been given. There was a diffuse increase of connective tissue throughout the liver between the individual trabeculae and liver cords, producing a certain amount of secondary atrophic degeneration of the liver cells. In places this process had gone on to complete the replacement of large areas of liver tissue and might even be consistent with a former acute toxic hepatitis such as acute yellow atrophy or eclampsia. There was marked bile duct and liver cell regeneration in the fibrosed areas. There was a moderate amount of bile stasis, but it was not symmetrically distributed and was readily differentiated from the tumor pigmentation.

The tumor feature of the pathologic condition of the liver was characterized by the presence of large masses of blackish-brown pigment in the form of granules which had been deposited extensively in the interstitial connective tissue. Some of it had been taken up by endothelial phagocytes. Much of it occurred in granular form in the tumor cells. This tended to confuse the picture somewhat. The tumor cells were polygonal and spindle cells. Many of these cells were in the sinuses and were with difficulty distinguished from the normal Kupfer cells which also could be found containing pigment. In many places there appeared to be some tendency toward alveolar formation by the tumor cells. Mitoses were found occasionally. Identification of the pigment was attempted by special staining reactions. Hemosiderin was ruled out by the Prussian blue reaction; hemofuchsin, by its special fuchsin stain; bile, by its reaction with the chrome salts, leaving melanin. This was further confirmed by staining with silver by Levaditi's method and by oxidizing with ferric chloride. Thus, by elimination, the tumor had to be considered as a melanotic sarcoma.

The regional lymph nodes draining the liver contained similar pigmented granules, some in tumor cells, but mostly occurring free in the peripheral sinusoid or taken up by endothelial phagocytes. No other metastases were found in any of the other tissues.

Sections through the spleen histologically were characterized chiefly by congestion of the sinuses. The follicles were atrophic in appearance.

The pancreas showed extensive postmortem degeneration. In addition, there was some evidence of obstruction to the outflow of its secretion, with dilatation of the pancreatic ducts. This resulted in moderate fat necrosis. There was extensive fatty infiltration of the pancreas, with atrophy of much of the acinar tissue. This left a number of the islands of Langerhans isolated in the fat. These had undergone some hyperplasia, almost appearing as small adenomas.

The gastro-intestinal tract was normal except for postmortem autolytic degeneration.

The kidneys were characterized chiefly by early vascular lesions with slight secondary degenerative changes involving both glomeruli and tubules. In addition, there was a definite hemorrhagic pyelitis with effusion of blood under the mucosa. This was not accompanied by any cellular reaction.

The suprarenals were negative except for postmortem autolytic degeneration.

Histologically, the genitalia showed simple senile atrophy.

The pathologic diagnoses were melanotic sarcoma of the liver (? primary); chronic progressive (Laenec's) cirrhosis, atypical; splenomegaly; acute pyelitis; chronic fibrous pancreatitis with fat necrosis; early chronic progressive vascular nephritis.

Comment.—This case is one of unusual interest, as it presents certain features unlike those of any other melanotic tumor which I have been able to find in the literature, with one exception—a case mentioned by Hanot and Gilbert [12] in their monograph on diseases of the liver. Ewing, in his "Neoplastic Diseases," quotes Rolleston as referring to nine cases reported as primary melanoma of the liver. He also mentions a case of Johnston's, which Elser [13] recorded, of a large pigmented tumor of the liver with no demonstrable primary tumor found elsewhere. It resembled more definitely, however, the usual picture of metastatic melanotic sarcoma, although of a diffuse nature.

This tumor, unlike any of the other so-called primary melanomas of the liver, had an almost uniform distribution of the pigment throughout the liver substance without any suggestion of nodule formation. It was accompanied by a marked atrophic cirrhosis with numerous areas of capsular thickening. There were no discrete tumor nodules anywhere in the liver. On section it bore a striking resemblance to a piece of granite. Histologically, the tumor cells were found in the stroma, in the sinusoids and in the portal areas essentially equally. They consisted for the most part of large mononuclear cells which ranged from polyhedral to spindle in form, and which contained varying amounts of pigment. Much of the pigment was free in the interstitial tissue spaces. The clinical history is of interest in that no symptoms occurred suggesting a primary melanotic tumor elsewhere in the body. It is not impossible of course to have overlooked a minute pigmented tumor of the choroid, or of the brain; but there was nothing in the liver to suggest that the tumor there was of a secondary metastatic character, and no metastases elsewhere could be found.

At no time did the physical examination of the patient or the subsequent examination at necropsy reveal any potential tumor nodule or pigmented nevus which could be considered as a possible primary focus. The first impression one received of the liver, on gross examination, was that it was going to prove to be another case of cirrhosis hepatitis anthracoides, first described by Welch,[14] as the pigment was so black that it suggested carbon rather than melanin. Special staining methods to identify the pigment were used. The iron stain showed that it was not

12. Hanot and Gilbert: Étude sur les maladies du ioie, Paris, 1888.

13. Elser: Ewing's Neoplastic Diseases, Ed. 2, 1922, p. 693.

14. Welch, W. H.: A Case of Cirrhosis Hepatis Anthracotica, Bull. Johns Hopkins Hosp. **2**:32, 1891.

hemosiderin. Bielschowsky's silver nitrate method showed definitely that the pigment was melanin and not carbon, as did other tests with various bleaching agents, such as hydrogen peroxide, which slowly decolorized the granules.

The tissue was submitted to a number of well-known pathologists, including Dr. James Ewing, Dr. S. Burt Wolbach, Dr. Frank B. Mallory, and Dr. J. Homer Wright, all of whom agreed that it represented an atypical melanotic sarcoma, but some of whom were not willing to accept its primary character in the liver. It seemed unusual enough and of sufficient interest, however, to record as a probable case of primary melanotic tumor of the liver, not unlike the primary melanotic tumor of the spleen described several years ago by Ewing, for by elimination no other diagnosis is left.

I have made a careful search of the literature, and with the exception of Rolleston's [15] and Marx's [16] papers, which are covered briefly by Ewing, nothing has appeared during the past two decades. In the earlier literature a number of cases were reported, but as Hale White, Marx and Rolleston observed, most of them lacked some vital data, and most of them have to be discarded.

Hanot and Gilbert discuss the problem as it appeared to them in 1888. They felt that the development of the metastases in melanotic sarcoma had a dual etiology: (1) actual migration of the tumor cells, and (2) the transportation of pigment granules which they claimed had a definite combined action of producing toxic changes in the cells and of stimulating both phagocytosis of the Kupffer cells of the liver and a protective connective tissue proliferation, which led to the development of cirrhosis. On this basis the tumor I present may well represent a secondary metastasis, but the difficulty lies in the establishing of a primary focus for the pigment production, in explaining the localization in the liver and in proving the attractive hypothesis concerning toxicity and migration which they so dogmatically express.

The interesting thing from my point of view is the fact that as far as I can ascertain no comparable case has occurred in thirty-nine years, and that there are less than a dozen cases of primary melanomas of the liver altogether whose claim may be considered. One of the great difficulties in the earlier cases apparently was the differentiation of hemochromatosis from this condition, and even the differentiation of diffuse hemosiderosis or melanosis complicating malaria from tumor formation.

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15. Rolleston, H. D., and Treyor, R. S.: Primary Sarcoma in a Cirrhotic Liver, J. Path. & Bacteriol. **15**:249, 1910.

16. Marx, H.: Ueber einem eigenartigen primären Tumor der Leber (cf. Chorionepithelioma), Beitr. f. path. Anat. und allg. Path. **36**:585, 1904.

Again, the question of whether these tumors should be classified as sarcomas or carcinomas is of some academic interest. On the basis of Hanot and Gilbert's theory, it is not impossible to consider this tumor as an atypical diffuse primary carcinoma of the liver with secondary melanosis. This seems highly improbable, however, and I firmly believe that it represents a true primary melanotic sarcoma of the liver, and that accordingly it contributes in a small measure to the theory of the mesothelial nature of melanotic tumors arising from wandering or strayed chromatophores.

CASE 4.—The family history of Mrs. Catherine C., aged 36, in the service of Dr. F. H. Lahey, was of interest only in that her mother died at the age of 34 of "breast trouble." The marital history was not remarkable. She had been married sixteen years, and had had five pregnancies and one miscarriage. Her general health had been good. She had averaged 140 pounds (63.5 kg.) in weight for the past four years. She had had an occasional headache and had been troubled for several years by constipation. The menstrual history had not been abnormal.

For about six months she had noted indefinite pains across the lower part of the abdomen, which seemed increased by any physical effort. The pain had become progressively more and more severe. For about five months she had been conscious of a mass in the left upper quadrant of the abdomen. Accompanying the pain there had been some frequency of micturition with burning. For the past few months her periods had been irregular.

Physical Examination.—This was essentially negative, except for the presence of a tumor mass in the left upper quadrant, which suggested an ovarian cyst. An exploratory operation was advised.

Operation and Course.—A midline suprapubic incision was made. An ovarian cyst the size of a large watermelon was found involving the right ovary. It was removed easily, having a narrow pedicle and no adhesions. On the left side, there was a small polycystic ovary. The cysts were incised and their lining curetted. The uterus was suspended. A routine appendectomy was performed.

The patient made a satisfactory operative recovery and did fairly well for the first week, but complained of general discomfort. During the course of the next week she developed marked anemia and received blood transfusion. She ran a slight temperature, ranging around 100 F., but accompanied by a steadily climbing pulse. Following the transfusion she improved temporarily. She was seen in consultation with Dr. G. R. Minot, and a mass was felt in the abdomen in the region of the spleen. Owing to atypical cells in the blood smear, the question of leukemia was raised, but it was thought that the chief trouble was due to internal hemorrhage. A few days later, another transfusion of 500 c.c. was given. This again temporarily improved the condition of the patient, but within a few days she again began to grow worse rapidly. A third transfusion was given five days later. No noticeable improvement was shown, and she died the following day.

Necropsy.—The body was that of a well developed, undernourished woman of about 36 years. The pupils were regular and equal, each measuring 4 mm. There were no palpable, cervical or axillary lymph nodes. The chest was symmetrical, the breast tissue being atrophic. There were two scars in the

abdomen, one to the left of the midline measuring 23 cm. and extending 7 cm. above the umbilicus, the other starting at the level of the umbilicus 2 cm. to the right of the midline, measuring 13 cm. in length. The scar on the left had had the stitches removed. The one on the right was more recent and showed only beginning granulation.

The primary incision was made from the manubrium to the symphysis, disclosing a moderate layer of subcutaneous fat measuring 3 cm. on an average over the abdominal wall, and somewhat pale musculature.

The peritoneal cavity contained about 4 liters of bloody fluid containing very little fibrin clot. There was a dense reddish discolored tissue immediately under the peritoneum and apparently representing the omentum which was filled with blood clot which had undergone partial organization. This extended down into the pelvis to the stump of the right fallopian tube and ovarian pedicle. No evidence of bleeding from this operative scar was noted. The uterus was suspended. The pathologic condition appeared to be restricted for the most part to the abdominal cavity.

The pericardial cavity contained no free fluid and no adhesions. The heart weighed 215 gm. The epicardial fat was not increased in amount. The endocardium was smooth and glistening, and there were no valvular defects. The myocardium was somewhat pale, but it was normal in consistency. The chief point of interest in the heart lay in the presence of a number of metastatic tumor nodules which were firm in consistency, grayish white, irregular in size and outline, and apparently infiltrating the myocardium. These did not have to the same degree the telangiectatic appearance of the other metastases.

The lungs were both markedly edematous and somewhat congested at their bases. There were also noted several tumor nodules most of them miliary in size, similar in consistency and appearance to the nodules found in the heart. There was one larger nodule measuring slightly more than 1 cm. in diameter, of the same general appearance as the liver nodules. On removing the sternum, the internal mammary veins on both sides were found to be completely thrombosed, as seen through the pleural surface.

The liver was not enlarged and weighed only approximately 1,200 gm. Its capsule was irregular. There were multiple small papillary nodules projecting through the capsule. These varied in size, but very few were more than 2 mm. in diameter. In addition, there were a number of blackish-red areas, some measuring as much as 2 cm. in diameter and covered by a smooth capsule, but which on section showed a cavernous arrangement with a yellowish, papillary appearing stroma and vascular spaces filled with blood. There was one of these on the inferior surface of the liver which apparently had ruptured, and probably represented the source of the hemorrhage. There was no gross evidence of bile stasis, and the gallbladder and ducts grossly were negative.

The spleen weighed 240 gm. Its capsule was covered by a rough, shaggy, fibrinous exudate representing organizing blood clot. On section it showed no gross abnormalities. It was deep purplish red; the follicles were made out fairly easily.

The gastro-intestinal tract showed no pathologic condition externally, except for the organizing blood clot on the peritoneal surface. There were a few miliary nodules in the submucosa, especially of the terminal ileum and colon, apparently representing tumor metastases.

The kidneys weighed 310 gm. together, and appeared essentially normal externally. Their capsule stripped readily, revealing a smooth surface. The normal ratio of cortex and medulla was present. The right kidney contained one small cyst near the periphery, measuring about 3 mm. in diameter. The medullae appeared normal. Calices and pelves were negative.

The suprarenals were of normal size, color, consistency and position.

The uterus was normal in size. Externally there were no palpable tumors. A few small cysts were found in the cervix. The endometrium appeared essentially normal. The uterus was more or less buried in tissue like that seen in the omentum. There was no evidence of pregnancy or tumor formation.

The aorta showed beginning atheromatous degeneration with the formation of multiple small yellowish-gray plaques. These were most marked about the openings of the abdominal branches. Practically all of the mediastinal, retroperitoneal and mesenteric lymph nodes were involved in extensive tumor metastases having the same gross telangiectatic appearance as the tumor tissue noted in the liver. These nodes varied in size considerably, many of them being as much as 3 cm. in diameter. The metastases appeared restricted to the lymph nodes and did not show any definite infiltration of the surrounding tissues.

The bone marrow was removed from the middle third of the right femur, and showed marked hyperplasia. A slight grayish color was noted which suggested a hyperplasia of the white cells of the marrow as well as the red cells. It was consistent with a simple severe secondary anemia with leukocytosis or with a definite disturbance of the myeloid tissue such as is seen in leukemia.

Microscopic Examination.—The sections through the tumor nodules in the ventricular wall of the heart presented essentially the same histology as the tumor elsewhere, except as modified by the more resistant structure. The cells tended to be polygonal to spindle shaped, with large nuclei containing a definite nucleolus. Many mitoses were found, some of them multiple, and the cells tended to show considerable phagocytosis. This was accompanied by atrophy, degeneration and necrosis of the musculature with a secondary polymorphonuclear infiltration. The heart muscle elsewhere appeared essentially normal.

Sections through the lung metastases were similar in appearance except that they assumed the more vascular form, being complicated by extensive hemorrhage. There was some tendency for the cells to outline cavities which were filled with red cells. Here and there, the walls of these sinusoidal spaces showed proliferation of the lining cells with similar multiple mitoses and phagocytosis as were noted in the heart. There was a secondary bronchopneumonia and bronchitis associated with these metastases. Other portions of the lungs presented evidence of emphysema, edema and congestion, with a suggestion of fibrosis, chiefly peribronchial in distribution.

Sections microscopically through the tumor nodules in the liver presented evidence of a diffuse invasion of the parenchyma. The most striking feature of the pathology was the intimate relation of the tumor to the vascular endothelium, especially of the sinusoids. Everywhere a metaplastic tendency was noted for the endothelial cells to swell up and develop into typical large mononuclears, many of which were capable of extraordinary phagocytic activity. Here and there some suggestion of vascular channel formation was noted, but no striking vessel formation such as is seen in the capillary hemangiomas of the skin. The tumor invaded the liver cords, producing necrosis. Hemorrhage complicated the picture. The tumor cells invaded the portal areas, usually as narrow cords or as single cells. Primitive cells were seen whose origin could not be determined. Rare fused cells or multinucleated cells were encountered, but they were different in appearance from the usual carcinomatous giant cells. There was marked degeneration of the persistent liver tissue with extensive fatty metamorphosis. There was some periductal lymphocytic infiltration. In

the larger tumor nodules, there were great vascular areas in which individual primitive atypical appearing cells were seen, apparently for the most part cast off from the lining endothelium, as many of them could be found adherent to the wall. Mitoses were present in relatively large numbers, perhaps one to two per high power field; some were atypical in appearance. No apparent relationship to the liver cells other than that of invasion could be made out. It is impossible also to state absolutely, from the microscopic preparations, whether or not the tumor was primary in the liver or even whether it was definitely of endothelial origin.

Sections through the spleen were characterized chiefly by tremendous engorgement of the sinuses which practically obliterated the normal land marks. Here and there were foci of small lymphocytes representing follicles. There was evidence of metastasis even in the spleen, with a similar proliferation and arrangement of the tumor cells.

Sections through various levels of the intestine presented evidence of marked autolytic degeneration of the mucosa. There was one small tumor nodule which had a similar structure.

There was moderate vascular change in the smaller arteries of the kidneys but no marked evidence of arteriosclerosis. The glomeruli appeared normal. The tubules showed varying degrees of postmortem degeneration. There was some increase in the interstitial connective tissue. There was moderate congestion, and a few foci of hemorrhage were found.

There was considerable postmortem degeneration of the pancreas, which otherwise appeared normal.

The suprarenals presented evidence of diffuse tumor infiltration and secondary postmortem degeneration changes.

There was moderate hyperplastic endometritis of the uterus. The musculature appeared somewhat atrophic but otherwise normal. The left ovary showed no evidence of primary tumor formation. There were a few small follicular cysts and a corpus albicans. In the bone marrow there was a moderately active hematopoiesis, but no evidence of tumor formation.

The structure of the tumor was perhaps best made out in the lymph node metastases. The cells were rather nondescript, varying from definite spindle cells to large multinucleated giant cells of the typical tumor type. There appeared to be a definite tendency to form channels which were lined by these cells occurring for the most part in a single layer, but here and there heaping up to several cells deep. Phagocytosis was a prominent part of the picture. There was a great deal of necrosis and hemorrhage.

Sections through the omentum and mesentery presented the same diffuse infiltration by tumor tissue noted in the other organs. The picture was more obscured by hemorrhage and fat in this location, however.

Summary.—The combination of the gross and histologic findings of this case indicates clearly that death was due to a combination of internal hemorrhage and the usual toxic picture associated with malignancy. The histology indicates that this tumor was of sarcomatous rather than of carcinomatous origin. Several possibilities can be considered. The most probable of these is that the tumor was of endothelial origin, as no primary focus was found. The cells behaved very much as endothelium, forming giant cells and engaging in phagocytosis. A second possibility is that of mesothelial origin, possibly from the peritoneum. This is an attractive theory but difficult to prove. The tumor might conceivably be considered as an atypical primary hepatic carcinoma of the diffuse type. It does not appear to be either a sarcoma of fibrous tissue or lymphocytic origin. For purposes of classification, it may perhaps best be considered as an endothelial or angiosarcoma.

The pathologic diagnoses was: angiosarcoma of the liver with metastases to the heart, lungs, mediastinal, retroperitoneal, and mesenteric lymph nodes, suprarenals and spleen; intra-abdominal hemorrhage from rupture of the liver tumor; organizing hemorrhagic exudate of the peritoneum, omentum and mesentery; perisplenitis; periphepatitis; acute splenic tumor; hyperplastic bone marrow; anemia; thrombosis of the mammary veins.

Comment.—This case is presented because of its unusual character and the great difficulty of classification which it offers. The sections were submitted to the same pathologists as in the previous case, and a variety of opinions were obtained. The only point in complete agreement is that the tumor obviously was malignant. Ewing, in a personal communication, said that he was inclined to feel that more probably it was an atypical carcinoma, and he refers[17] to the paragraph in his book in which he has so succinctly expressed his opinion regarding the group of so-called "angiosarcomata" of the liver: "I do not believe, therefore, that the existence of a true angiosarcoma arising from blood vessels of the liver has been satisfactorily demonstrated. The structure in Marx' case is exactly duplicated by areas in l'Esperance's (case of multiple hemorrhagic) hepatoma." The other men whose opinion has been asked are all inclined to feel that it is a sarcoma rather than a carcinoma; and, as Wolbach has said, "the burden of proof is on those pathologists who wish to dispute the diagnosis." In this connection it is of interest to note that since writing this paper Dr. Stafford Warren has encountered apparently a parallel case of necropsy at the Massachusetts General Hospital, even to duplicating the cardiac and lymph node metastases. I have not yet had the opportunity of seeing the sections, however.

In general, this tumor seems to be most prominent in relation to the blood vessels and sinusoids, but the tumor cells infiltrate the liver tissue so diffusely that in many areas it is difficult to tell where liver ends and tumor begins, as can be seen from the various photomicrographs. Most of the blood vessels showed marked metaplasia of their endothelial lining cells, some of which were cast off into the lumen and could be seen demonstrating a phagocytic capacity of an unusual degree. Various suggestions have been advanced in attempting to explain the development of this tumor and to ascribe a nomenclature which would be satisfactory. Obviously, because of the definite nodules in the liver, and of the metastatic tumor masses in the lymph nodes, the heart and lungs, the question of where the primary focus arose has to be considered. It is not impossible that such a focus was overlooked, although necropsy was performed with that particular point in view, and it was only after prolonged search, particularly of the pelvis, that the conclusion was

17. Ewing: Neoplastic Diseases, ed. 2, New York, W. B. Saunders Co., 1922, pp. 675-701.

reached that it was probably a tumor of endothelial origin, with unusually diffuse manifestations. Unfortunately, the abdomen and pelvis presented so much hemorrhage and organization of the blood clot that a satisfactory examination of those tissues was impossible.

Personally, I feel that the tumor was probably of endothelial origin. This opinion is based on the fact that the most marked lesions were those associated with the endothelial lining of the sinuses and blood vessels, not only in the liver but in the lymph nodes, lungs and cardiac metastases. In the second place, no epithelial or connective tissue tumor of the liver of which I have any knowledge ever shows a phagocytic action in the least comparable to that found in this particular tumor, a reaction which is characteristically one of the outstanding functions of the endothelial leukocyte.

The principal argument against the tumor being of endothelial origin is that almost no evidence of true capillary blood vessel formation is noted. This argument has been advanced in support of the epithelial origin of this tumor, the feeling in this instance being that the tumor is so diffusely infiltrated by these inflammatory phagocytic cells as to confuse the picture and offer an opportunity for misinterpretation.

L'Esperance's [18] case, already cited, perhaps more closely simulates the tumor reported here than any of the other recorded cases. Her article is an admirable summary of our present knowledge of this group of tumors, and is noteworthy also for a complete and invaluable bibliography. In conclusion she states that "the evidence appears very strongly to favor an epithelial origin for these atypical tumors, and it seems advisable, therefore, to classify them with the primary diffuse carcinoma from liver parenchyma. The term 'atypical hemorrhagic malignant hepatoma' seems most suitable."

SUMMARY

Four unusual malignant tumors involving the liver are presented: (1) a primary hepatoma in a girl of 10, (2) a metastatic leiomyosarcoma in a woman of 50, (3) a primary melanoma of the liver in a woman of 68, (4) a probable angiosarcoma in a woman of 36.

In view of the comparative rarity of these tumors, a discussion of each case is presented with a review of such literature as could be found in relation to them.

The cases are presented principally for purposes of record, that an understanding of their etiology and behavior may be reached ultimately when a sufficient number have been made available for study in this manner.

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18. L'Esperance, E. S.: Atypical Hemorrhagic Malignant Hepatoma, J. M. Res. **27**:225, 1915.

PLATE 1

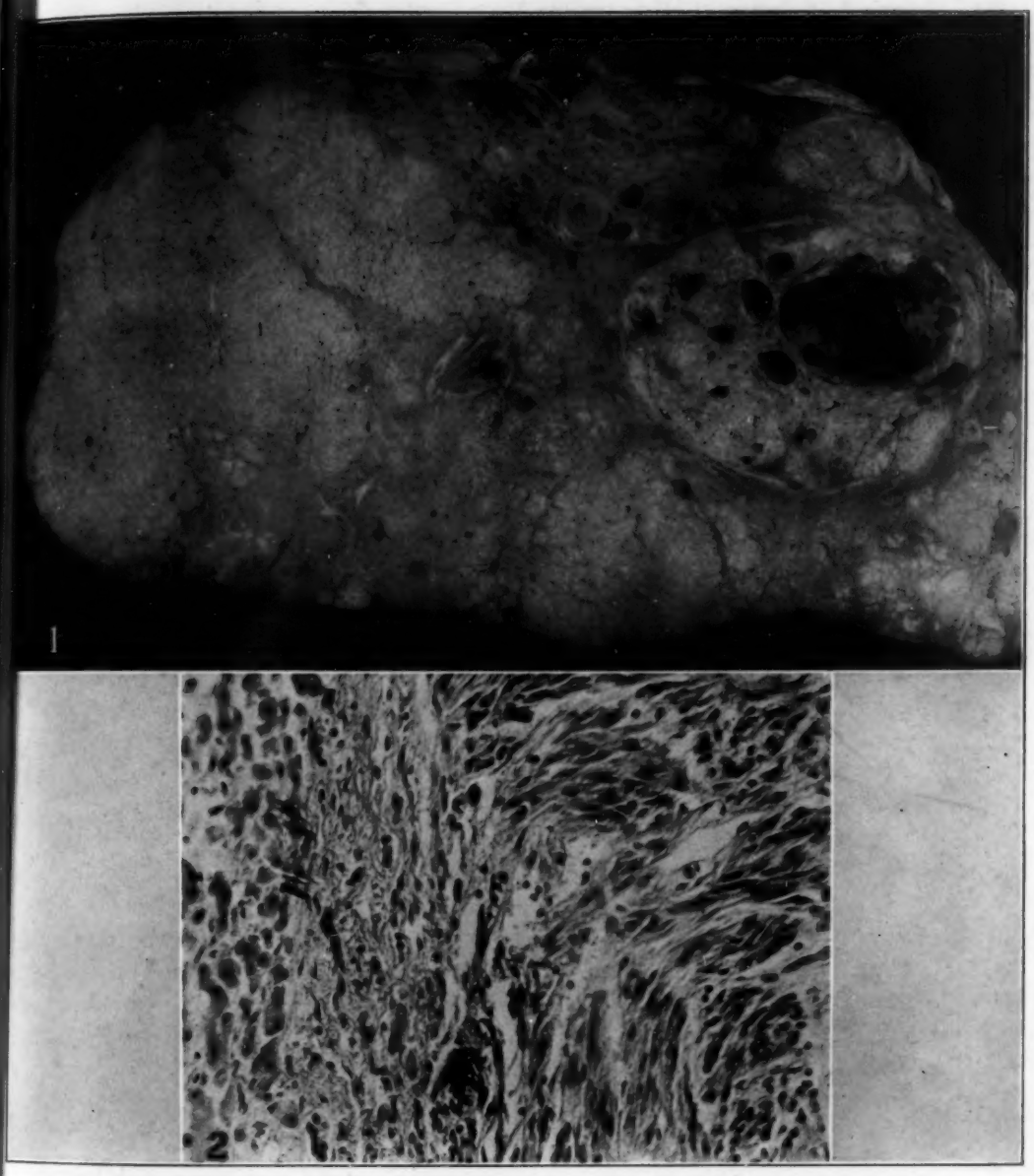


Fig. 1 (Case 1).—Cross section of liver; gross specimen. Note diffuse nodular appearance of tumor growth, the venous invasion and the cirrhosis.

Fig. 2.—Low magnification (Leitz objective, no. 16, ocular no. 2) of typical smooth muscle tumor encroaching on liver tissue.

PLATE 3

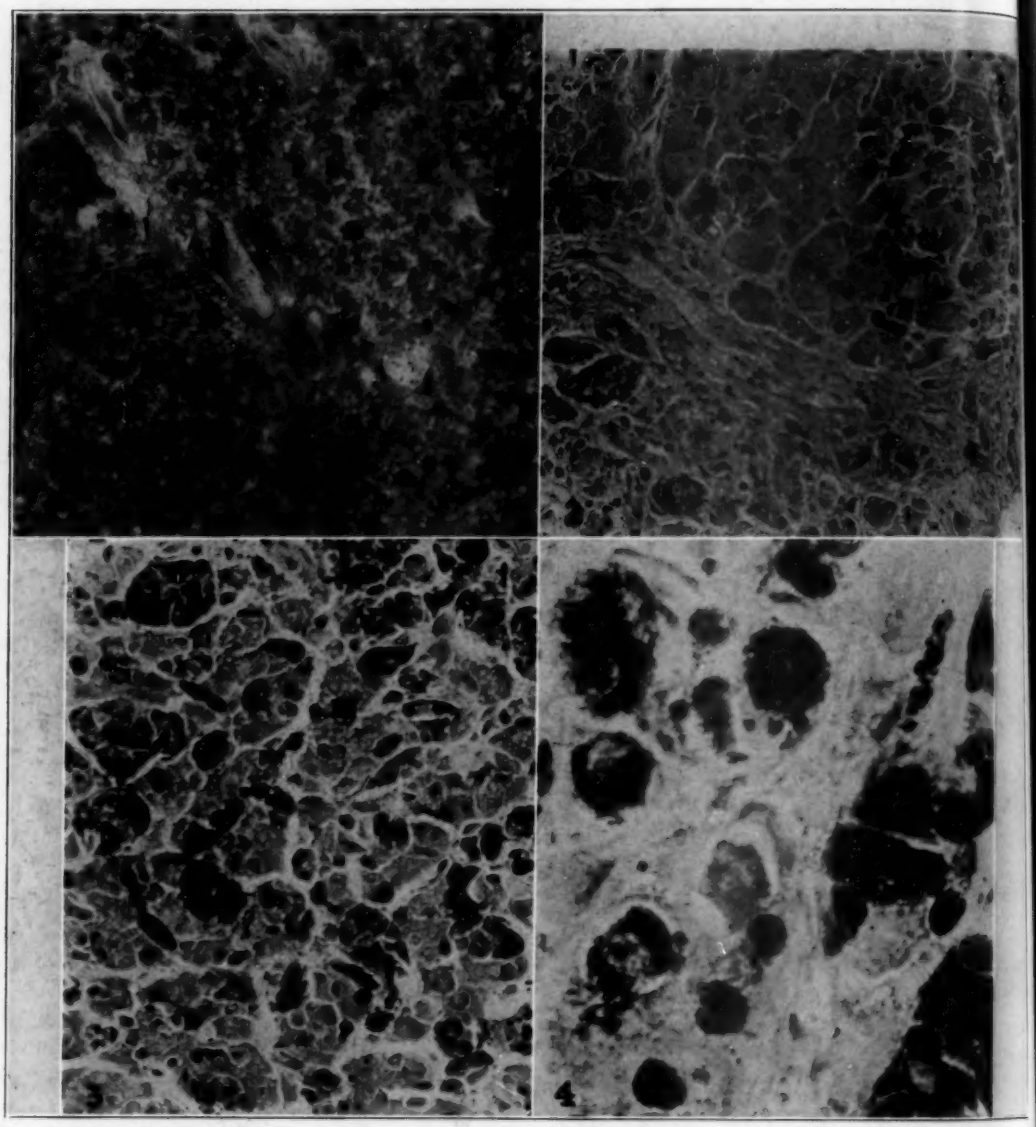


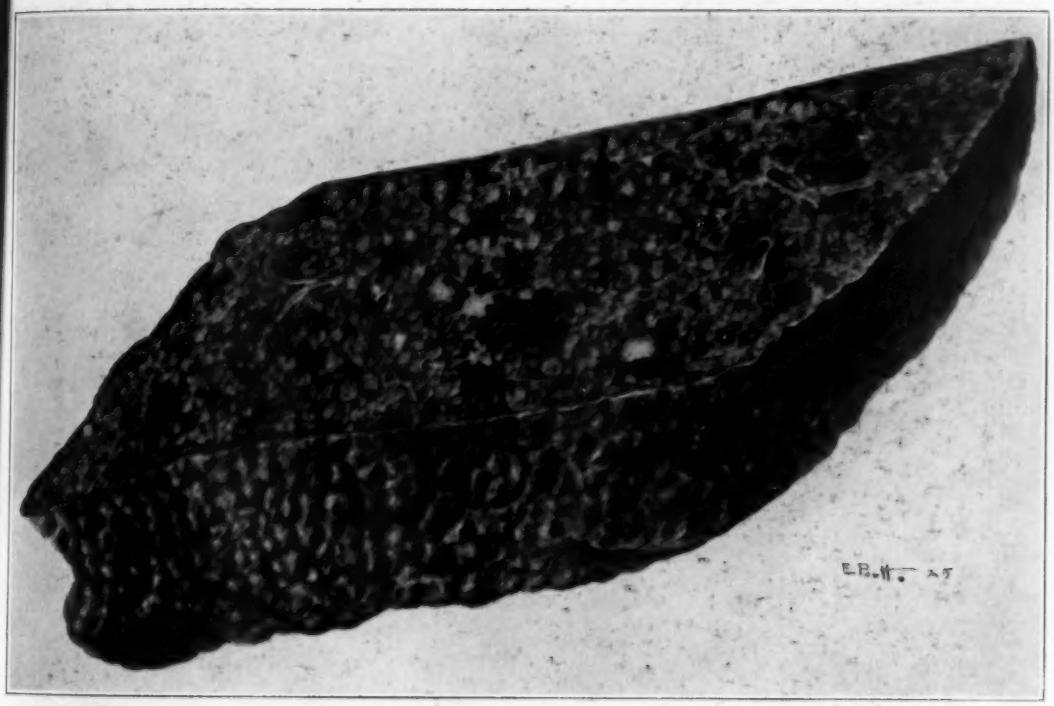
Fig. 1.—Low magnification of liver from case 3.

Fig. 2.—Low magnification (Leitz 16 mm. objective and no. 2 ocular) of diffuse infiltration of tissues.

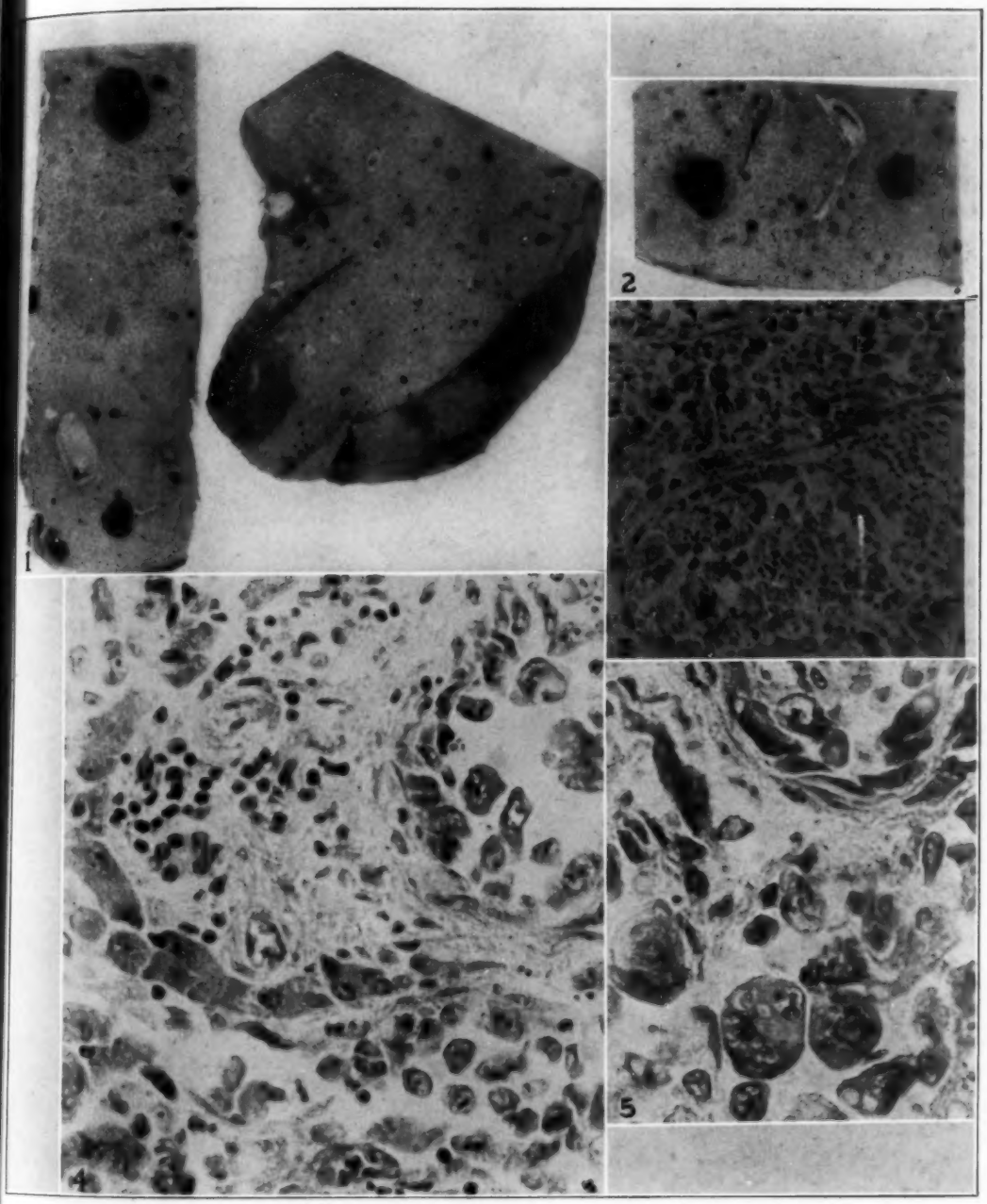
Fig. 3.—Higher magnification of figure 2 (Leitz 16 mm. objective, no. 4 ocular).

Fig. 4.—High magnification (Leitz 4 mm. objective, no. 4 ocular) illustrating tumor and phagocytic cells with pigment granules, also free pigment in tissue spaces.

PLATE 2



Liver from case 3. This illustrates the "granite"-like appearance due to the diffuse infiltration of stroma, parenchyma and sinusoids by the tumor cells. The thickened capsule and the hobnailed, cirrhotic, contracted appearance is also shown.



Figs. 1 and 2.—Cross sections of liver showing tumor in nodules in case 3.

Fig. 3.—Lower (Leitz 16 mm. objective, no 2 ocular) magnification illustrating diffuse involvement of tissues.

Fig. 4.—Medium (Leitz 8 mm. objective, no. 4 ocular) magnification showing the obvious vascular origin of the tumor and its diffuse character.

Fig. 5.—High (Leitz 4 mm. objective, no. 4 ocular) magnification of the phagocytic tumor endothelial cells, showing the relation to blood vessels.

RECURRENT LIPOMATOUS TUMORS OF THE GROIN

LIPOSARCOMA AND LIPOMA PSEUDOMYXOMATODES *

WITH TWO PLATES

RICHARD H. JAFFÉ, M.D.

CHICAGO

Malignant tumors derived from fat storing cells are rare. Although a number of cases have been reported, the clinical course and the structure and nature of these tumors are still a matter of discussion. The existence of a true liposarcoma has even been considered doubtful by some investigators (Schwalbe, Ribbert).

The classification of malignant lipomatous tumors is complicated. No doubt certain new-formations have been termed liposarcoma, without sufficient evidence to warrant this diagnosis. Sarcomas springing from the stroma of a lipoma such as fiber cell or spindle cell sarcomas should be excluded; also those tumors in which fat tissue is associated with cartilage, bone, or especially myxomatous tissue, the latter structures giving rise to atypical growth. In these mixed tumors, fat often plays only a passive rôle.

There are also tumors which consist of fat cells different from those predominating in typical benign lipomas. They resemble embryonic fat cells (lipoblasts), and at times mature fat cells are entirely absent. The elements of these tumors are large and small cells, which show all the different stages of fat storage, from the segregation of finest lipoid granules to the formation of large fat drops (Razor,[1] Cornolle,[2] Koritschoner[3]). One must, however, bear in mind the fact that immature fat cells are common in benign lipomas, and that in some of these tumors they may be numerous. They form the only way by which a lipoma can grow, the mature fat cells being unable to proliferate (Ribbert,[4] Ewing[5]). If we consider these tumors as sarcoma, we shall encounter certain objections, since, as a rule, they are encapsulated and can easily be removed, and since the histologic structure is regular, and cell anaplasia or atypical mitoses are absent. Though some observers have noted an invading growth into the adjacent musculature (Koritschoner, Cornolle), nothing is known about recurrence or metastases.

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* From the Department of Pathology, University of Illinois, College of Medicine and the Uihlein Laboratory of Grant Hospital.

1. Razor: Frankfürt Ztschr. f. Path. **14**:359, 1913.
2. Cornolle: Virchows Arch. f. path. Anat. **230**:68, 1921.
3. Koritschoner: Centralbl. f. allg. Path. u. path. Anat. **32**:145, 1922.
4. Ribbert: Geschwulstlehre, 1914.
5. Ewing: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1922.

It seems to me that the new growths made up of lipoblasts should rather be called lipoblastomas (Razor), and be separated from the liposarcomas, which show all the characteristic changes of a sarcoma, such as anaplasia of cells, rapid and destructive growth and production of metastases.

Making these restrictions, few cases have been observed which justify the diagnosis of liposarcoma. A true liposarcoma has recently been described by Caldwell and Zinninger.[6] It was found in the lumbar spinal canal of a man, aged 69. The tumor was attached to the external surface of the dura, where benign lipomas also occasionally occur. Necropsy was not performed, and the authors only mentioned a metastasis in the third lumbar vertebra.

LIPOSARCOMA

That a liposarcoma may sometimes prove malignant is shown by the following observation:

CASE 1.—A colored woman, aged 34, was operated on two years ago for a fast growing tumor of the left groin. In the laboratory report of the Presbyterian Hospital of Chicago, where the tumor was removed, it was described as coconut-sized, not encapsulated, white, friable, superficially ulcerated and covered with greenish-yellow material. The diagnosis was lipomyxosarcoma.

On Dec. 12, 1924, another operation was necessary, which again revealed a sarcomatous new-growth in the left groin.

The woman came to the Cook County Hospital on Jan. 7, 1925, complaining of pains and severe bleeding from the wound. She was well nourished, and the main objective finding was a foul-smelling wound in the left inguinal region, from which soft dark red masses protruded. The temperature was 102 F.; the white blood cell count 12,000; hemoglobin, 80 per cent. A trace of albumin was found in the urine.

On January 13, the patient coughed up a small amount of blood, but the physical findings in the chest were negative.

The tumor in the groin grew fast and bled profusely. The patient became progressively weaker, and died, Feb. 17, 1925.

Necropsy.—Necropsy performed by Dr. D. J. Davis revealed a well nourished woman, 180 cm. in length, 77 kilograms in weight. A large, foul-smelling, cauliflower-like mass protruded from the left inguinal region and extended upward to the symphysis. It measured 20 cm. in both diameters and was elevated about 8 cm. The tumor was attached to the fascia. The color was white, with areas of yellowish-green and reddish discoloration, especially near the surface. The consistency was soft and brainlike. A mucoid, grayish fluid could be removed from the cut surface. There was an old linear scar, 20 cm. long, to the left of the tumor, which was completely healed.

The tumor had invaded the left femoral vein, and soft, grayish-white masses completely filled its lumen. The masses extended downward 15 cm. below Poupart's ligament and upward to about 2 cm. below the union of the venae ilicae.

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6. Caldwell and Zinninger: Surg., Gynec. & Obst. **40**:476, 1925.

There was bilateral acute serofibrinous pleuritis. The lower lobe of the left lung contained an irregular, soft, yellowish-gray mass, 7 to 10 cm. in diameter, from which gray strands radiated in different directions. About the bronchi of this lobe there was much brainlike, soft substance, which was also found in the bronchial lumen. Similar masses were observed in the pulmonary veins. The bronchial lymph glands were small and calcified.

The heart weighed 255 gm. There were acute thrombo-endocarditis of the pulmonary and bicuspid valves and acute parenchymatous degeneration of the myocardium. The liver weighed 1,900 gm.; there was fatty change. The spleen weighed 95 gm.; the pancreas weighed 95 gm. The right kidney weighed 160 gm.; the left kidney, weighed 161 gm. There was cloudy swelling.

There were intramural and submucous fibromyomas of the uterus; the largest tumor measured 6 cm. across.

The heart blood revealed hemolytic streptococci. Exudate from the pleura and pus from the bronchi yielded hemolytic streptococci and *Staphylococcus aureus.*

Microscopic Examination.—The microscopic picture of the tumor was characterized by an enormous number of fat droplets, which filled the bodies of irregular cells. There was only one type of cell that showed a certain uniformity. It closely resembled a normal fat cell and contained a large drop of neutral fat, which replaced most of the cytoplasm and pushed the nucleus toward the periphery. In some places these cells predominated, while in others they were mixed with cells which were of such different size, form and structure that no two cells were alike. There were small round or oval cells, with round, dark nuclei and with fine lipoid granules. All the intermediary stages could be observed between these forms and very large cells, from 100 to 120 mikrons in diameter, which were distended by huge fat drops (Fig. 1). Their nuclei were large and irregular; they lay in or near the center, and were surrounded by fat drops. The chromatin was very coarse, forming bulky masses with vacuoles. In Figure 1 a nucleus is pictured with a granular framework of chromatin. The clear spaces are vacuoles. Sometimes the nuclei stained diffusely, or they appeared broken up into smaller round, oval or angular pieces Mitoses were not found. Although most of the large cells were crowded with fat, there were occasional cells which showed relatively few lipoid droplets in the acidophilic cytoplasm (Fig. 2).

Most of the fat gave the microchemical reactions of neutral fat. It stained orange with sudan; pink with nile blue sulphate; it was not optically active and did not stain with Lorrain-Smith-Dietrich's method.

Some of the smaller droplets were complicated mixtures of phosphatids and cholesterol esters. They became more numerous near the place where the tumor tissue was necrotic. The larger droplets sometimes showed a membrane of double refracting lipoids, or they contained bundles of fine needles of cholesterol esters.

Besides the fat, two other kinds of cell inclusions were observed. They occurred in the same cells together with the fat droplets; when they were large, the fat could be reduced to a few small granules. These cell inclusions formed round, hyaline droplets and coils of fibers. The droplets were homogeneous; their diameter was from 2 to 14 mikrons, and they were separated from the surrounding protoplasm by an unstained space. They stained bright red with eosin, yellowish-red with Van Gieson and black with Heidenhain's iron hematoxylin stain. With Mallory's connective tissue stain they appeared dark blue, yellow or brown. The difference in the staining affinities does not depend on

the size of the droplets. Small droplets may stain blue, yellow or brown, and a similar coloring may be observed in the larger drops.

The coils of fibers were enclosed in large vacuoles (Fig. 3). The fibers were highly refractive and resembled fibrin. This resemblance was confirmed by the staining reactions, which were as follows: eosin: bright red; Van Gieson: yellow; Mallory: bright yellow; Heidenhain: black; Weigert's fibrin stain: dark blue. When the vacuoles containing the fibrin-like bundles reached an extreme size, they burst, and part of the fibers escaped into the intercellular spaces.

The tumor cells were surrounded by a fine meshwork of reticular fibers, which became denser about the numerous capillaries. The capillaries were often distended or passed into free accumulations of blood cells.

The free surface of the tumor was necrotic. A coarse meshwork of fibrin was visible between the amorphous cell débris and the fragments of broken-down nuclei. Necrotic areas were also found in other parts of the tumor. The blood vessels in or near the necrosis were closed by fibrin clots.

In some places the tumor cells shrank, became small, flattened and branched, while a homogeneous or fine granular substance with distinct affinity to the hematoxylin appeared between them. This substance stained purple with cresyl-violet, but gave no reaction with mucicarmin, mucihematin and thionin.

The examination of the metastases in the lung yielded findings identical with those of the primary tumor. The mucoid degeneration was pronounced. The tumor masses frequently occluded the pulmonary veins (Fig. 4) or filled the lumen of smaller bronchi whose walls were almost completely destroyed, the cartilage alone remaining visible.

The diagnosis in this instance was relatively simple, the tumor being a sarcoma with extensive fat deposits in the cells. The question as to the significance of the fat in regard to the histogenesis of the tumor cells will be discussed later.

LIPOMA PSEUDOMYXOMATODES

That difficulties sometimes may arise in interpreting the microscopic findings of a recurrent lipomatous growth is shown by another tumor that was removed from the inguinal region of a white woman, aged 41.

CASE 2.—The patient reported that she had been operated on twice for fatty tumors in the left groin. The last operation was two years before, after which roentgen-ray treatment was given. A new tumor developed within a few months. The third operation was performed on June 30, 1924, by Dr. Beers, at the Grant Hospital of Chicago. A lobulated mass 10 by 5 by 7 cm. in diameter was found in the subcutaneous tissue of the medial part of the upper third of the left thigh. The surgeon noticed during the operation that the tumor contained peculiar looking firmer parts, and that it was adherent to the fascia. I was called in consultation, and since the macroscopic appearance was suggestive of sarcomatous degeneration, a radical operation was advised. The mass, together with some of the fascia, was removed as completely as possible. The wound healed without complications.

Macroscopic Examination.—The tumor formed an irregular mass of small and large, soft, yellow lobes. Bundles of firm grayish-white tissue in circumscribed places were attached to the tumor.

On cross section, two types of tissue could be distinguished. The periphery was yellow, slightly translucent and showed a distinct lobulation, the lobules being separated by firmer grayish tissue. In the center there were several

PLATE 1

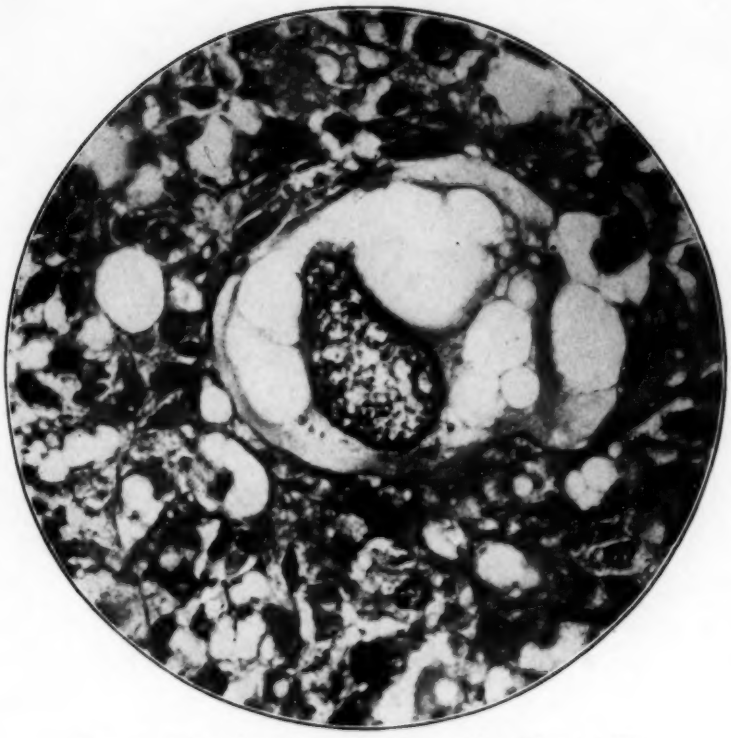

Fig. 1.—Giant fat cell. Hemalaun-eosin stain; × 275.

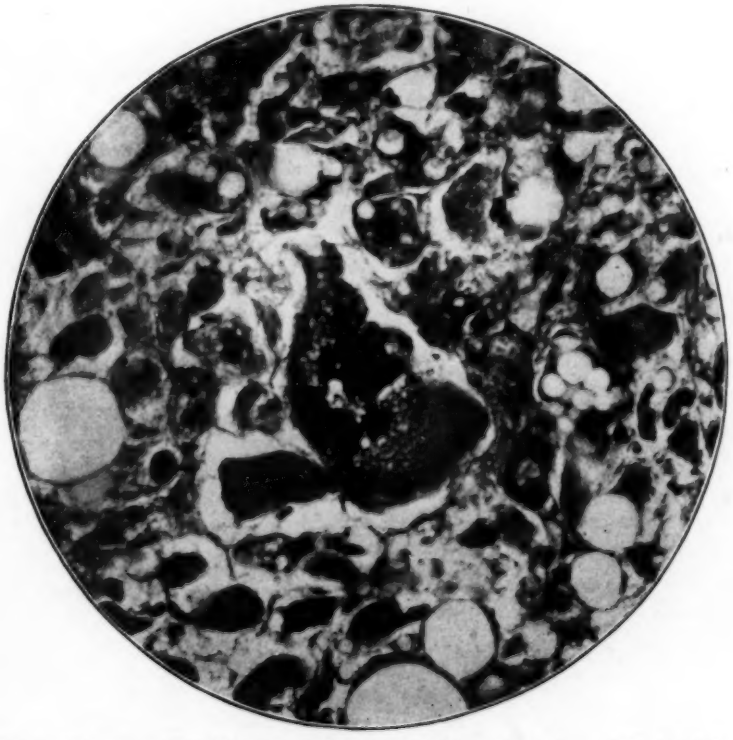

Fig. 2.—Large cell with two pyknotic nuclei and a few fat droplets and granules. Note the typical fat cells, besides the atypical ones in the surrounding areas. Hemalaun-eosin stain; × 275.

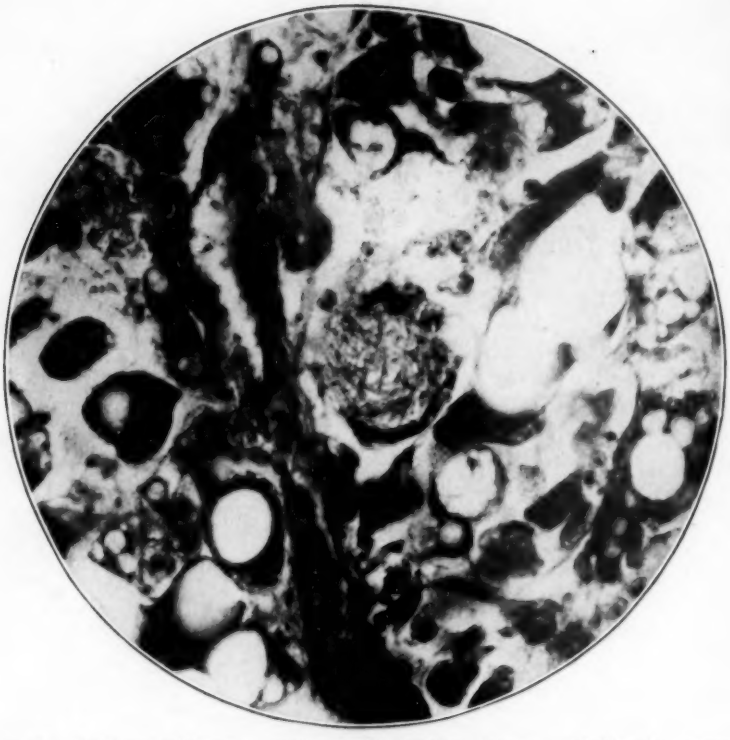

Fig. 3.—Cell containing a coil of fibrin-like fibers. Mallory's connective tissue stain; × 500.

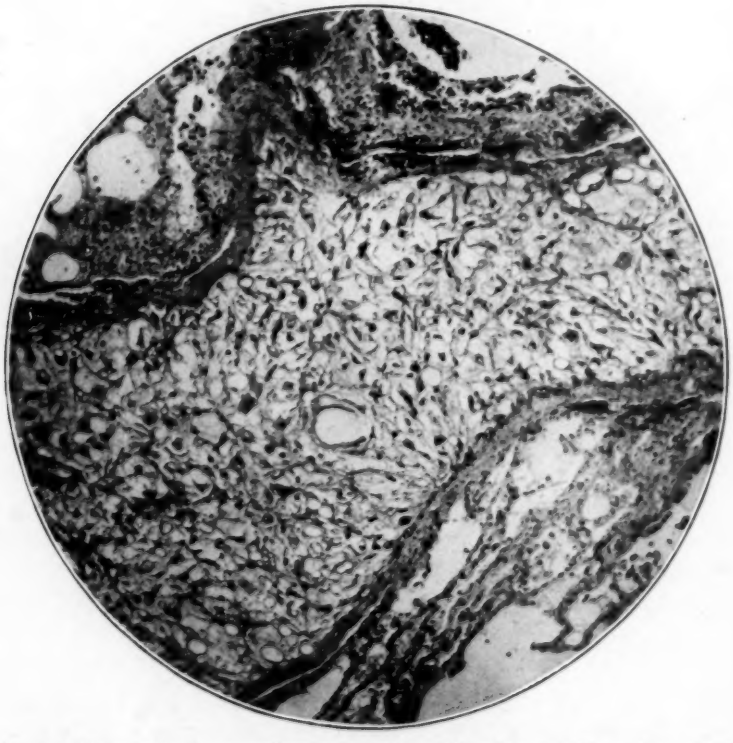

Fig. 4.—Metastasis in a pulmonary vein. Hemalaun-eosin stain; × 65.

spherical nodules of rubber-like consistency, 3 to 5 cm. in diameter. Their cut surface was smooth, gray and somewhat glassy. It resembled colloid. The two parts of the tumor were sharply demarcated from each other.

Microscopic Examination.—The lobulated yellow part of the tumor was formed by groups of large round and oval fat cells, which were separated by thicker bundles of connective tissue with small arteries and veins.

The glassy, translucent nodes consisted of a loose basal substance in which cells of various sizes and forms were embedded. The cells tended to form compact areas, between which there were only a few small cells. The basal substance contained bundles of very fine fibrils and many capillaries. It stained pale blue with hematoxylin and gave a weak metachromatic coloration with thionin and cresyl-violet, which was not more pronounced than that occasionally observed in edematous connective tissue.

The cells were elongated or rounded and often possessed branches that connected nearby cells, thus producing syncitia-like structures. In some places the cell outlines were more distinct. The nuclei were large, oval, pale and contained from 1 to 3 deeply stained nucleoli.

Fat stains revealed fat droplets in all cells. Some had only a few small granules and droplets in the cytoplasm about the nuclei; others were crowded with larger drops, which also filled the branches. Finally, some cells resembled typical mature fat cells. Free fat droplets of different sizes were also found.

The two types of tumor tissue gradually passed over into one another. Bundles of spindle-shaped, oval and round cells arranged about blood vessels appeared between the fat cells of the peripheral parts separating them to form small groups and to lie as isolated cells. The cells contained varying amounts of lipoid droplets, and the fat cells fused with them, so that it is hard to say whether they broke down and became replaced, or whether they became transformed.

In the places in which the fascia was attached to the tumor, the syncitia-like, lipoid-carrying cell masses with the mucoid intercellular substance were found between the dense bundles of collagenous tissue. Arrosion of blood vessels was not observed.

The diagnosis was lipoma pseudomyxomatodes.

The patient returned to the hospital exactly one year after the last operation. A swelling had again developed in the left inguinal region, which consisted of a soft tumor, about 6 to 8 cm. in diameter in the subcutaneous tissue underneath the scars left by the former operations. The tumor was removed, and had a gross appearance like the former specimen. There was only one colloid node measuring 3 by 3 by 2 cm., which was covered by numerous fat lobules. The microscopic picture was practically identical with the description already given.

COMMENT

The two tumors described were located in the inguinal region. A survey of the literature reveals that most of the atypical lipomatous tumors have been found in the lower half of the body, especially in the groin and in the upper part of the thigh.

In the first case, a diagnosis of lipòsarcoma was made, but proof is still lacking that the fat content of the tumor cells warrants this diagnosis, and that it is not due to degeneration or to an invading growth into fat tissue.

Fatty degeneration is frequently found in rapidly growing malignant tumors; but the occurrence of typical fat cells in addition to the abnormal anaplastic cells, and of intermediary stages between the two kinds of cells, is in favor of the origin of the tumor from fat storing elements. Besides, fatty degeneration does not lead to the formation of those atypical giant fat cells, which are the most striking feature in this case. Finally, the chemical nature of the fat, which was found to be mainly neutral fat, also confirms this diagnosis.

The possibility of a phagocytosis of preexistent fat by the proliferating cells is excluded by the fact that a great deal of fat has also been observed in the metastases of the lung.

With regard to the mucoid changes, I would say that they are only degenerative, and that they are nct essential in the classification of the tumor. Typical myxomatous tissue is absent. The fibrin-like substance found in some of the cells seems to be a peculiar type of abnormal intracellular aggregation of an apparently degenerative nature.

The persistently recurring lipomatous tumor of the second case is characterized by circumscribed areas of a mucoid tissue, and the question arises as to the significance of this tissue.

Mixed tumors composed of mucinous and fat tissue are not rare. Robertson,[7] in 1916, collected fifty-one cases from the literature, 33 per cent. of which were malignant tumors, and added one new observation. The most common localization of the myxolipoma is the intermuscular tissue of the lower extremities (43 per cent.).

In the new growth under discussion, the resemblance to mucinous tissue was limited to the gross appearance, and the microscopic picture was not in accord with the diagnosis of lipomyxoma. The intercellular substance, though giving some of the microchemical reactions of mucous, was, no doubt, edematous connective tissue. It contained bundles of collagenous fibers, and the cells embedded with it were not stellate cells, but fat cells which were shrinking and breaking down. The fat-carrying cells predominating in certain areas were different from the cells of a myxoma. They were branched, but they contained much more fat than mucous cells do. The large pale nuclei with the distinct nucleoli were similar to the nuclei of young, immature fat cells.

While mucoid degeneration was common in larger lipomas, it is to be noted that the mucoid parts of the tumor described here were not simply areas of degeneration, but were the centers of growth, as is evident from the groups of young, immature fat cells. The close relation between mucinous and fat tissue during embryonic life explains the observation that fast growing immature fat cells sometimes resemble mucinous cells without really being transformed into them.

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7. Robertson: J. Med. Res. **35**:131, 1916-1917.

On account of these considerations the tumor is termed lipoma pseudomyxomatodes. The word sarcoma has been avoided, because the cellular structure does not justify this diagnosis. However, the rate of growth, the persistent recurrence and the infiltration of the fascia indicate that special attention should be given to this form of lipoma.

CONCLUSIONS

The groin and the upper part of the thigh seem to be the most common seats of the atypical lipomatous tumors.

Three different types of these tumors are distinguished: First, the lipoblastomas which consist of immature fat cells. They are usually benign because they do not recur and form no metastases. Second, fast growing tumors with a tendency to recur. The fat cells they are composed of are immature and atypical, forming syncytium-like structure and producing a mucoid intercellular substance. The name, lipoma pseudomyxomatodes has been suggested for these tumors. Third, liposarcomas which are characterized by a pronounced anaplasia of the fat storing cells, by persistent recurrence, by invasion of blood vessels and by metastases.

Laboratory and Technical Notes

THE MEINICKE MICROREACTION IN SYPHILIS*

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In recent years many attempts have been made to diagnose syphilis by a method which would be specific in character and have a more simple working basis than the Wassermann reaction.

In 1917, Meinicke and Sachs-Georgi proposed a test for syphilis based on a white precipitation when an alcoholic extract of a normal heart was added to the blood serum of a syphilitic person. Since this was not a true precipitin test from a biologic standpoint, it has been called a floccule formation test. The early flocculation tests, however, had many disadvantages, and the procedure was not altogether simple. The length of time required was from twenty-four to forty-eight hours, and gave rise to erroneous results on account of bacterial contamination. In many cases the reading was indefinite. In the course of years most of the objectionable features have been eliminated, and Meinicke, in his third modification, using tulol balsam extract of horse heart, demonstrated that a turbidity precedes the floccule formation. This takes place within an hour and is easily recognized by the naked eye.

The nature of the floccule formation as well as the Wassermann reaction is as yet not entirely understood. Meinicke considers his test to be a true immunity reaction, depending on a specific antibody.

The ordinary Meinicke[1] test is carried out in the following manner: Two tubes, one containing 1 cc. of the Meinicke extract, the other 10 cc. of a 3 per cent sodium chloride solution, are kept in a water bath at a temperature of 45 C. for ten minutes; then extract and salt solution are mixed and used immediately for the test. One part of the patient's serum, and five parts of the freshly mixed extract dilution are measured into a small test tube, shaken and kept at room temperature protected from light for one hour. After that time the negative specimens are found unchanged, and the positive specimens have become almost opaque when held up to the window screen in daylight.

In a recent publication Meinicke describes a microreaction. In all tests for syphilis heretofore large quantities of blood serum were necessary. A microreaction has been attempted with the Wassermann and Sachs-Georgi tests, but has not been found practicable. Meinicke saw in his method which required no inactivation of the blood serum a much better chance for a microreaction.

The blood can be obtained from the ear, one drop being drawn up into a tube of 10 cm. in length and 1 to 2 mm. in width. Then one end of the tube is sealed if the examination is to be made in the same place, otherwise

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* From the State Psychopathic Institute.

* Read before the Chicago Pathological Society, December, 1925.

1. Meinicke, E.: Meinicke Microtest for Syphilis in Children, Med. Klin. **21**:123-134 (Jan. 25) 1925. Dohnal: Technic of Meinicke Microreaction, Dermat. Wchnschr. **80**:367 (March 7) 1925; **80**:408 (March 14) 1925. Schükri: Meinicke's Turbidity Reaction, München. med. Wchnschr. **72**:183 (Jan. 30) 1925.

both ends need to be sealed. After coagulation has taken place, this tube is centrifuged and the part of the tube containing the clear serum is separated from the rest by means of a glass file and is then ready for use.

To 600 cc. of a 3 per cent solution of sodium chloride 0.1 Gm. of sodium carbonate is added. Of this dilution 5 cc. are measured into one test tube and 0.5 cc. of the Meinicke extract into a second test tube. Both tubes are put into a waterbath of 45 C. for ten minutes. The warm extract and the sodium solution are mixed quickly. A cover glass preparation is now made, using one small platinum loop full of blood serum to one large platinum loop full of diluted extract. The large platinum loop must be of such a size as to hold exactly five times as much as the small loop. Serum and extract are thoroughly mixed on the cover glass, and a hanging drop preparation is made. The slide is kept in the dark at room temperature of not more than 20 C. for one hour, when the reading can be made under the microscope with a high dry lens. In negative specimens the field looks almost empty; here and there a few dancing spots are seen. In positive specimens definite clumping has taken

Findings with Wassermann and Meinicke Tests

Wassermann Test		Meinicke Test	
Negative	799	Negative	799
Positive	111	Positive	111
Anticomp	9	Negative	9
Anticomp	13	Positive	13
Doubtful	8	Positive	8
Doubtful	7	Negative	7
Negative	13	Doubtful	13
Positive	5	Doubtful	5
Negative	19	Positive	19
Positive	16	Negative	16

place, giving a similar picture to the positive Widal reaction. Instead of the platinum loops method, which may become inaccurate easily, leukocyte pipets have been used.

Meinicke recommends not to make more than ten preparations with the same extract dilution, as on long standing an opacity may be produced giving a false positive reaction.

The reading should be made at the end of one hour; a second reading may be made after another hour, but a longer delay is likely to cause unspecific changes which render the results a good deal more indefinite and even false.

Of 1,000 specimens of blood serum which were tested by both the Wassermann and the Meinicke methods, my results were:

Of the nineteen cases that were negative with the Wassermann and positive with the Meinicke reaction, eleven had a history of syphilis or had had a positive Wassermann reaction a few years before. Eight specimens of the thirteen specimens from the tuberculosis hospital were doubtful with the Meinicke and negative with the Wassermann reaction. Of the sixteen cases with a positive Wassermann and a negative Meinicke reaction, eleven were cases of general paralysis in which the patients had received two years of intensive treatment with tryparsamide and sulpharsphenamine. This treatment had been discontinued two weeks prior to the tests.

The Meinicke test both in the macroscopic or microscopic method is especially valuable when the Wassermann test is anticomplementary or doubtful. Most of the blood serums we are handling are sent in from a distance and are several days old before reaching us. Occasionally some have become slightly anticomplementary or hemolytic. In a fairly large number of persons with syphilis of long standing, the kind that are likely to be admitted to the state hospital, a negative or doubtful Wassermann test on blood serum is not uncommon, while in many the Meinicke test is positive.

SUMMARY

The advantage of the microscopic over the macroscopic Meinicke test is the easier detection of floccules and the minute quantity of blood serum necessary. The microscopic test requires accuracy and a room temperature not above 20 C. (70 F.). In experienced hands it is a valuable adjunct in the diagnosis of syphilis.

AN ERROR IN ACID-FAST AND GRAM STAINING DUE TO PETROLATUM*

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An interesting observation was made while I was at the Johns Hopkins University, in the department of pathology and bacteriology, in which a smear made from the pus of a pleural infection showed what seemed to be acid-fast bacteria. These bacteria were most probably only artificially made to appear acid-fast by the presence in the smear of petrolatum transferred by the swab from the edges of the skin about the discharging sinus.

A patient with a thoracic empyema had had a resection of a rib, and a granulomatous growth had developed at the site of operation as well as a sinus discharging a purulent fluid from the empyematous cavity. There was some suggestion that the granuloma was tuberculous, and a smear was made from the purulent fluid and stained by the Ziehl-Neelson method. After a prolonged search a group of red staining bacteria was found. These bacteria were not morphologically typical of human tubercle bacilli, and it was provisionally suggested, because of their short length, that they might be of the bovine type. After a further study of the slide no other acid-fast bacteria were to be found, but there was noted a number of groups of similar short diphtheroid bacilli which had not retained the fuchsin stain. More material was obtained from the patient; injections were made into animals, cultures were made, and more stained smears were studied. Tuberculosis did not develop in the animals. The cultures yielded a variety of bacteria, among them a diphtheroid bacillus suggesting that seen in the original smear. The second direct smears did not show any acid-fast bacteria, with the exception of one bacillus which was free from the slide and floating in the immersion oil.

These findings suggested that we might be dealing with an artefact, and before the animals could be examined a number of experiments were carried out in an attempt to find an explanation for these results. Suspecting that petrolatum may have been used on the skin edges of the sinus, I placed on a

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slide a small amount of petrolatum album, then smeared the slide with some of the isolated culture of the non-acid-fast diphtheroid bacillus, and made a Ziehl-Neelson stain. I found that the diphtheroids retained the fuchsin stain in the region where the petrolatum had been placed. This was repeated many times, with similar results. On inquiry I learned that petrolatum had indeed been used on the skin edges in connection with the Carrel-Dakin treatment of the patient mentioned.

A further study of this phenomenon has been carried out, and the purpose of this report is to indicate briefly some of the conditions under which it may occur and the results of my attempt to discover an easily used remedy for this possible error in the interpretation of stained smears.

Having established that a particle of petrolatum on a slide afterward smeared with bacteria caused the bacteria to take on the character of acid-fastness, I tried the same method using gram-negative bacteria and the Gram method of staining. It was shown that many of these bacteria took on gram-positive as well as acid-fast characters, but apparently not so many were affected as with the gram-positive bacteria. This is probably due to the fact that the stains used are less penetrating. It was found that more of the organisms become covered with the petrolatum, particles of it practically being absent on the slide when it was stained, if the bacteria are thoroughly mixed with the petrolatum before smearing. This is probably what would occur if the swab absorbed petrolatum from the skin in the taking of material, and this were rubbed on the slide before staining.

The film of petrolatum, which I presume is formed, is resistant to various decolorizing agents commonly used in different methods of the acid-fast staining. I found that the petrolatum treated bacteria after steaming with carbol-fuchsin were not decolorized by repeated washings with acid alcohol, 10 per cent sodium sulphite, acetone and Gram's iodine solution or different solutions of sulphuric acid to 33 per cent or of nitric acid to 25 per cent followed by 95 per cent alcohol.

In an attempt to find a satisfactory treatment for removing the petrolatum, experimentally added or accidentally present with the bacteria or other material on the slide, a number of solvents were studied. In the United States Pharmacopeia, 1926, petrolatum and petrolatum album are given as insoluble in water, almost insoluble in cold or hot alcohol and in cold dehydrated alcohol. They are freely soluble in benzene, carbon disulphide, chloroform and oil of turpentine; soluble in ether, petroleum benzene and in most fixed or volatile oils, depending on the composition of the petrolatum. I tested a number of solvents on smears of mixed bacteria and petrolatum and found xylol to be the most satisfactory. Benzene did not remove the film on all the bacteria after one washing but did after three washings. Its inflammable nature makes it inadvisable for use. Chloroform gave an incomplete result after three washings. Ether was even less effective, as was acetone, and carbon tetrachloride was ineffective. Xylol cleared the smear of all acid resisting bacteria after two or three treatments. After two washings with xylol followed by the acid-fast staining method a few bacteria were possibly a pale pink, but after three washings with xylol no resistant bacteria could be found. Xylol was used at different stages of the staining method, and it did not give as good results after the carbol-fuchsin had stained the petrolatum covering the bacteria. However, after the stained smear has been dried, xylol will readily remove the stained petrolatum.

It is therefore proposed that all smears be washed thoroughly with xylol before using the acid-fast or gram stain when the material to be examined

may have petrolatum or other similar compounds accidentally mixed with it on the swab or slide. Xylol is not very inflammable, but of course must be kept away from the free flame of the bunsen burner.

Petrolatum is widely used by surgeons on the edges of wounds to prevent irritation in the Carrel-Dakin and other treatments, as a lubricant for catheters and for many other purposes. Bacteriologists frequently employ petrolatum to prevent oxygen absorption for anaerobic cultures. Under all these circumstances a possible danger of faulty staining is present.

A number of other fatty substances besides the yellow and white petrolatum were tried. Butter fat, meat fat, cream, ear wax and glycerin were applied in the same way as the petrolatum but without any apparent coating of the bacteria, and the tests were not continued. These few substances were chosen because of certain obvious possibilities of error in examining milk, discharges from the ear and other cavities as well as the use of glycerin as a lubricant for catheters. I would suggest that the lubricant used by urologists be tested for this phenomenon.

REVIEW OF THE LITERATURE

Smears from saliva treated with petrolatum and stained with the Ziehl-Neelson method showed that some of the large epithelial cells became acid-fast, and recalled a paper by Milligan[1] in which he said that "the finding of large numbers of flattened polyhedral 'acid-fast' squames (epithelial cells) is diagnostic of cholesteatomatous degeneration" in middle ear infections. It is a point worth considering whether there may not be fatty changes in tissue which, altering the staining characters of certain cells, may set free substances capable of affecting chance bacteria in the tissues so that their staining response will be different.

In 1886, Bienstock[2] and Gottstein[3] reported a change in the staining characters of a number of non-acid-fast bacteria by growing them on butter agar so that they became acid-fast. Campbell[4] could find no confirmation of their work in the literature, and repeating it did not obtain the same results. He used cultures of *B. prodigiosus, B. typhosus, B. proteus* and *B. mucosus-capsulatus,* and cultured these on glycerol-broth-agar to 5 cc. of which had been added and thoroughly mixed [illegible]cc. of the lipoidal substance, butter, hydrous wool fat or beeswax. Transfers were made every forty-eight hours for sixteen weeks, and no evidence of acid-fast characters appeared in any of these cultures when the precaution was taken to wash the smear two or three times with ether before staining. When this treatment with ether was left out, in many instances isolated bacilli or even clumps were found to stain by the Ziehl-Neelson method. These bacilli retaining the fuchsin stain did not stain solidly but appeared to have a fatty capsule, and Campbell considered that the earlier workers were dealing with occluded lipoids. I found with petrolatum that the staining was uniform throughout and showed no evidence of a capsule formation and, if diphtheroids were used, closely resembled forms of *B. tuberculosis.* The film of petrolatum presumably formed must be extremely thin, but is uniform in distribution.

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1. Milligan, W.: Brit. M. J. **2**:972, 1907.
2. Bienstock: Fortschr. d. Med. **4**:193, 1886.
3. Gottstein, A.: Fortschr. d. Med. **4**:252, 1886.
4. Campbell, L. K.: Acid Fastness in Non-Acid-Fast Bacilli, Am. Rev. Tuberc. **11**:450, 1925.

Cedercreutz[5] studied the conditions of the Gram method of staining along somewhat the same lines. He used butter, white of egg and white starch. He placed a drop of butter on a slide and immersed the bacteria in this. The slide was then warmed and the excess butter fat poured off. He found two of his gram-negative cocci stained as gram-positive. *B. coli* also gave a gram-positive stain but somewhat weaker; the gonococci remained gram-negative. Butter added to agar and used as a culture medium gave the same results. The bacteria became gram-negative when transferred to plain agar. Starch paste only affected the two cocci, and white of egg changed them but slightly. He considered that the results were not due to purely physical causes. Schmidt[6] noted that fatty stools of infants showed a preponderance of gram-positive colon-like bacilli in contrast to those with a low fat content. He found that *B. coli* became gram-positive (Weigert) when grown on butter-agar-gelatin. A slide smeared with butter and then *B. coli* did not change the staining character of the bacillus. The bacilli also grew on the butter medium in longer forms than they did on plain agar. He further said that defatting the slides did not alter his findings.

CONCLUSIONS

Smears made from wounds or other infections, when petrolatum has been used as part of the treatment, should be treated with xylol or some other active solvent before they are stained.

If petrolatum is used on catheters, the chance of error in searching for tubercle bacilli should be recognized.

Smears from anaerobic tubes in which petrolatum is used on the surface of the medium should also be thus treated before differential staining.

Animal inoculation or culture remains the best method for finally determining the presence of *B. tuberculosis*.

Other lubricating substances used on catheters or in treatment should be tested as to their ability to confer on bacteria this acid and alcohol resistant character.

The fatty substances formed in tissue in certain degenerations or other changes should be tested for this characteristic.

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5. Cedercreutz: Studies on the Conditions of Positive and Negative Results of Gram Staining by Some Bacteria, Arch. f. Dermat. u. Syph. **93**:369, 1908.

6. Schmidt, A.: Zur Kenntniss der Bakterien der Säuglingsfaeces, Wien. klin. Wchnschr. **5**:643, 1892.

General Review

HODGKIN'S DISEASE*

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The present conception of Hodgkin's disease as a histopathologic entity is the result of a process of splitting up of the complex group of pathologic conditions reported by Hodgkin in 1832. In that year he described seven cases, all of which had in common a widespread swelling of the lymph glands of the body, enlargement of the spleen and liver, anemia, cachexia and death. Hodgkin called attention to a clinical syndrome rather than to a definite pathologic lesion. In 1845, Virchow separated this group into a leukemic and aleukemic subgroup when he identified the leukemias. From the aleukemic subgroup, Cohnheim, in 1865, separated pseudoleukemia, a condition which he defined as having the gross and microscopic pathology of lymphatic leukemia without the leukemic blood picture. In 1893, Kundrat described lymphosarcoma, thus separating another entity from the still composite group of aleukemic lymphadenoses. Finally, Sternberg in 1898 and Reed in 1902 gave accurate descriptions of the histopathologic complex now recognized under the name of Hodgkin's disease.

During the period between 1856 when Wilks gave the name "Hodgkin's disease" to the clinical syndrome and the publication of the papers of Sternberg and Reed, numerous cases of this condition were reported under such a variety of names that in 1899 Sternberg was able to collect seventeen titles that had been applied to it. More names have been given to it since that time. The more important and commonly used of these names are lymphadenoma (Wunderlich), malignant lymphoma (Billroth), lymphogranulomatosis (Paltauf, 1909), and malignant granuloma (Benda). The synonymous use of "pseudoleukemia" and "Hodgkin's disease" has led to much confusion.

In this review the name Hodgkin's disease will be used in the same sense as it was employed in the classical paper of Reed (1902). There are numerous objections to such terminology, but until we know more of the etiology and nature of the disease, a name that is already in common use has some advantages, as long as it is kept clearly in mind that it connotes a definite histopathologic concept. This usage has the further support that it is the term employed in the "Index Medicus."

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In 1911, both Ziegler and Fabian wrote monographs on this subject and collected the literature to that date. This review will, therefore, deal almost exclusively with contributions to the literature since 1911.

THE NATURE OF HODGKIN'S DISEASE

Differences of opinion as to the nature of Hodgkin's disease range from the dogmatic assurance of Sternberg (1898) to the frank agnosticism of Ewing (1923), who is "impressed with the utter obscurity as to the origin and clinical significance of Hodgkin's disease."

Sternberg (1898) was convinced that Hodgkin's disease was "a peculiar type of tuberculosis of the lymphatic apparatus running the course of a pseudoleukemia." Reed (1902), Longcope (1903) and others agreed that it is an infectious granuloma, but denied that the etiology was tuberculous. Clarke (1901) pointed out that Hodgkin's disease resembles an infectious process in the following ways: (*a*) It exists in acute and chronic forms, the acute type sometimes running a very rapid course; (*b*) the disease may remain localized for years, then become generalized and rapidly fatal; (*c*) the lymph glands most frequently affected are those which are most easily infected through the skin or mucous membranes; (*d*) it is specific for one particular tissue, namely, the lymphadenoid tissue; (*e*) its mode of spread is usually from the affected gland to those nearest; (*f*) it is often accompanied by a recurrent type of fever; (*g*) in the final stages there is cachexia, and often diarrhea, hemorrhages from mucous membranes and pyrexia, as in the final stages of a septicemia; (*h*) finally, the disease has the histologic appearance of an infectious process.

Before Sternberg and Reed gave to Hodgkin's disease a definite histologic character, numerous authors classed the condition among the tumors. For our present purposes it is necessary to consider only the reports in the literature since 1898 which deal with well authenticated cases. Gibbons was convinced that Hodgkin's disease was a neoplastic process. In the discussion of his cases he took up Clarke's points one by one and showed that either they were not universally true of all cases, or that they might just as well be applied to certain types of tumors. He pointed out that Hodgkin's disease frequently invades the capsules of the glands and the surrounding tissues; insisted that it has not been proved that the so-called metastases originate only in pre-existing lymphoid tissue and not from cells transported thither; and saw a resemblance to sarcoma in the irregularity of arrangement of its cells, in the numerous large mitoses indicating that the cells proliferate in situ, and in the possession of a stroma similar to that in sarcoma; and, finally, he declared that the giant cells in Hodgkin's disease resemble those of sarcoma more than those of an infectious granuloma.

Coley, Oliver, Tsunoda, Mallory, Warthin (1923) and others also consider Hodgkin's disease as neoplastic in character.

Mallory classes this disease as a lymphoblastoma of the slowly growing, scirrhous variety. "The type cell," according to Mallory, "is the lymphoblast, which occurs in some tumors as cells of large size, with large lobulated or multiple nuclei, which arise by mitosis, often multiple. Sometimes the tumor cells arouse marked reaction on the part of the fibroblasts, so that the latter multiply exceedingly, just as they often do in certain forms of carcinoma. This noticeable increase of connective tissue is most common in the slowly growing scirrhous type of lymphoblastoma. At the same time there is often an abundant infiltration with eosinophils and plasma cells. The distinguishing feature is the presence of tumor cells, often in very small numbers, which are different from any cell found in chronic inflammatory processes." But Delbet noted that it is not uncommon in Hodgkin's disease for the lymph glands to become rapidly enlarged all over the body, while a tumor begins in one place.

Another group takes a middle ground. Lubarsch (1918) thinks that Hodgkin's disease occupies a position between the infectious granulomas and the true tumors, and is differentiated by the fact that it is a system disease affecting the entire lympho-hemato-poietic apparatus. Levin (1919) also looks on it as a borderline condition between inflammatory processes and malignant tumors. It is not a degenerative process like syphilis and tuberculosis, but an active proliferation of all types of cells in the lymph glands. This proliferation, says Levin, is limitless and the cells are therefore "biologically identical with carcinoma cells." Levin (1923) is also convinced that the differences in the effects of irradiation will show that lymphocytes that may be morphologically identical may have different biologic characteristics. Mueller also recognized the close relationship of Hodgkin's disease to tumors, but apparently does not class it as neoplastic.

More recently Symmers (1917, 1924) has introduced a new conception of its nature. He declares that "Hodgkin's disease does not provide any criteria by which it may be grouped either among the inflammatory diseases or among the neoplasms." He believes that it is an affection of the "hemolytopoietic apparatus." Its histogenesis is determined (1) by preliminary hyperplasia of the lymphoid cells in various parts of the body, and (2) by the discharge of mononuclear and multinuclear giant cells from the bone marrow with or without eosinophils and eosinophilic myelocytes, and their arrest by the hyperplastic lymphoid depots in pursuit of their functions as filters, the fibroblastic reaction in the recipient tissues representing a mechanical process designed to support the excess of cells by which they are burdened.

The confusion which exists regarding the nature of Hodgkin's disease is due in large measure to our ignorance of its etiology. Such facts as we possess concerning the causation of this disease may now be presented.

ETIOLOGY

The distribution of Hodgkin's disease appears to be worldwide. Reports of it have come from practically all of the countries of Europe and North America. Aberastury, and Arrillaga have reported cases from the Argentine republic; Dias and Torres, from Brazil; Datta, from India; Abelheim, from South Africa; Bull, and Mathewson from Australia; Roberts, from New Zealand; and Seo, and Mitarashi, from Japan. Kraus and Lubarsch thought that they had noticed an increase in the number of cases in Berlin; but Fraenkel and Much (1918) could not confirm this for Hamburg.

Race does not appear to be an important predisposing factor. A far greater number of cases have been reported among the white races than among any others; but this might well be due less to racial susceptibility than to facilities for diagnosis and incentives to publication in the countries occupied by the white races. Negroes in the United States show a high morbidity and mortality from tuberculosis, and among them tuberculosis of the lymph glands is not uncommon. Hodgkin's disease occurs among them (Reed, 1902; Webster, and others) but reports of the disease in that race are by no means in proportion to those reported in white persons. But this again may be due to economic and social conditions and to geographic distribution rather than to any essential difference in racial predisposition. Bunting (1924) states that in his experience "the Jewish race would seem to show a somewhat heightened susceptibility to the disease."

Desjardins and Ford in 135 cases studied at the Mayo Clinic found the disease 2.3 times as common in men as in women. The series of collected, well authenticated cases by Ziegler, Fabian (1911), Fischer, Bunting (1924) and others, show approximately the same proportion.

Murray, and Hertz and Wretowsky have observed that parturition is followed by Hodgkin's disease in a few cases. Pregnancy appears to have an unfavorable influence on the course of the disease; it may become acute and rapidly fatal. Mellon (1916), McAlpin and von Glahn, Weber (1923) and Gemmell and others have noted cessation of menstruation very early in the course of Hodgkin's disease. This amenorrhea may be due to the accompanying anemia rather than to any direct effect of the disease. However, Gemmell believes that the occurrence of the disease in women is associated with hypofunction of the ovaries and in support of this view presents an analysis of fifty-seven cases in women.

Hodgkin's disease may occur at any age. Fabian (1911) mentions a case in a child 5½ months old. The oldest patient of whom I found a record was that of Fazio (cited by Ziegler), who was 76 years old. In the series of collected cases of Ziegler, Fabian (1911), Bunting (1924) and in 147 cases which I have collected, the third and fourth decades showed the greatest incidence of the disease. Kirschner and Lehndorf consider Hodgkin's disease especially malignant in children.

There is little definite information relative to the effect of occupation on Hodgkin's disease. Of twenty-six patients studied by Lemon and Doyle, sixteen worked outdoors and ten indoors. Social conditions appear to play no significant part, although Stengel thought that the disease was commonly associated with poverty; Gulland, with poverty and unfavorable living conditions. Murray considered those occupations and social conditions that are associated with exposure to cold, want of food, alcohol, overexertion or mental depression as conducive to the disease. It is to be noted that all of the conditions mentioned are also conducive to tuberculosis.

In Ziegler's opinion, "constitution" plays no important rôle in the etiology of Hodgkin's disease. Lichtenstein (1921) takes the opposite view because this is a system disease, affecting a particular tissue in the body. Fraenkel and Much (1923), who believe that Hodgkin's disease is a peculiar form of tuberculosis of the lymph glands, emphasized "constitution" as an important factor in determining whether the infection with tubercle bacilli will take the form of typical tuberculosis, or the atypical form with the histologic characteristics of Hodgkin's disease. They speak of the constitution being "tuned" so that it responds to the infection with a peculiar type of reaction.

Heredity could hardly be expected to be a predisposing factor in an infectious disease. Before Hodgkin's disease was accurately differentiated as a histologic entity, Mueller (1867) mentioned the disease as occurring in a man and all his children; and Degen (1886) reported it in two sisters, and Senator and Peacocke, in twins. The patients of Warnecke and of Steiger (1915) gave histories of other members of their families with enlargements of lymph glands. Braun reported the cases of three sisters between the ages of 45 and 47 who died of Hodgkin's disease; they came of a tuberculous family, and the diagnosis was not confirmed by necropsy. Reports of more than one definite case of Hodgkin's disease in the same family appear to be rare; and the instances cited in the foregoing might be explained as readily on the basis of opportunity for infection as on the basis of heredity.

Preexisting local disease has been assigned as a predisposing factor or as a portal of entry; e. g., otorrhea, nasal infections, pharyngitis (Trousseau); carious teeth (Trousseau, Rolleston); diseases of the upper air passages and mouth (Ruffin). Ely, Reed (1902) and Edsall

have recorded cases following whooping cough; Levy after pneumonia, and Edsall after measles and typhoid fever. Ziegler points out that malaria, rheumatism, pneumonia, etc., occurring years before the onset of Hodgkin's disease can hardly be considered as etiologic factors. Murray thought that tuberculosis of the lymph glands might predispose to Hodgkin's disease, and states that "in a few cases the onset of the disease was preceded by scrofulous enlargement of the glands with suppuration."

An antecedent syphilitic infection has been mentioned by Gowers, Hutchinson, Renvers, Vaquez and Ribierre, Iwanow, Fabian (1911) and Kawatsure. Rothe speaks of "pseudoleukemia on a hereditary syphilitic basis." But in none of these cases is there satisfactory evidence that the syphilitic infection was a factor in the development of Hodgkin's disease.

The significance of bacteria in lymph glands is not easily determined. Bloomfield found bacteria of various kinds in 29 per cent of apparently normal lymph glands and in 76 per cent of those that were definitely diseased. The mere presence of any particular type of micro-organism in lymph glands is not therefore necessarily prima facie evidence that that organism is the cause of the disease. Eight or ten different species of bacteria have been isolated from Hodgkin's glands and assigned an etiologic rôle in the disease. Only two of these have received serious attention, namely, the tubercle bacillus and the group of diphtheroid organisms, under the name of *Bacillus hodgkini*.

Before discussing these two micro-organisms and their claims to etiologic significance, a few more recent but as yet unconfirmed reports may be mentioned. Bramwell observed in specially stained sections of Hodgkin's glands small intracellular bodies which suggested protozoa. Vedeler saw intracellular and extracellular bodies which he interpreted as sporozoa. Brusa made similar observations. Kofoid and his co-workers have reported Hodgkin's disease in patients suffering from amebic dysentery. In the enlarged lymph glands they found bodies which they believed to be amebas, basing their opinion on (*a*) the structural characteristics of nucleus and cytoplasm; (*b*) the structure of the nucleus in mitosis, that in the ameba being distinctive and different from that in human cells; and (*c*) on the number of chromosomes, these being from three to eight times as numerous in amebas as in human nuclei. One of the cases in which they found these ameba-like bodies had been previously reported by Lincoln, and the histologic picture was peculiar in that the eosinophils were present in extraordinary numbers. Lamright has also reported a case of Hodgkin's disease associated with amebic dysentery. Fischer (1923) has taken exception to Kofoid's view of the possible relation of ameba to Hodgkin's disease. Infections

with pathogenic amebas are accompanied by the formation of pus, whether in the wall of the intestine or in the liver. This is not characteristic of Hodgkin's disease. Merk has recently reported the presence of some form of thallophyte in one case of Hodgkin's disease and insisted on its etiologic importance. Mosler speaks of "leprosy progressing under the picture of pseudoleukemia." Haberfeld also considers leprosy as a possible etiologic factor in Hodgkin's disease. Dias isolated from Hodgkin's glands a polymorphous fungus, pathogenic for guinea-pigs, rabbits and monkeys. He believed that this was the cause of the disease. The foregoing reports are recent and have not been confirmed.

Reference has been made to antecedent syphilitic infection as a possible predisposing factor in Hodgkin's disease. Galloway and Nanta have described cases of widespread syphilitic involvement of lymph glands. Bryant thought that the histopathology of Hodgkin's disease was often suggestive of syphilis. Löwenbach made careful comparative histologic studies of syphilitic and Hodgkin's lymph glands and pointed out certain similarities between the two conditions. Apparently with the support of Sternberg, he spoke of "a peculiar syphilitic disease of the lymph glands." The results of the Wassermann test in Hodgkin's disease have not supported a syphilitic etiology for that disease. Caan obtained a positive Wassermann reaction in two of four cases; Ziegler in one of four cases, and McAlpin (1923) no positives in fourteen cases and a doubtful reaction in three cases. In 1907, Proescher and White reported finding spirochetes in the lymph glands in a case of Hodgkin's disease; and the next year they found these micro-organisms in lymphatic leukemia. MacCallum (1907), Kidd and Turnbull, Longcope (1908), Weber and Ledingham, Moritz, and Karsner were unable to confirm the findings of Proescher and White.

Sternberg's paper (1898) was the first definite and successful attempt to separate Hodgkin's disease in the sense used in this review from ordinary tuberculous lymphadenitis on the one hand and from the aleukemic lymphadenoses on the other. The reports of Reed (1902) and Longcope (1903) confirmed and made more distinctive the histopathology of Hodgkin's disease, but both rejected Sternberg's view of its tuberculous origin. Sternberg (1909) himself has become somewhat less dogmatic on this point. But since the appearance of these three fundamental contributions to our knowledge of Hodgkin's disease, the chief point of dispute has been its relation to tuberculosis.

A widespread tuberculous infection of the lymph glands does occur. It is more common in children, but has been observed in adults (Askanazy, 1897; Dietrich, 1896; Courmont, Tixier and Bonnet). Patten and Bissell have described a form of tuberculous lymphadenitis

which appears to be peculiar to negroes. It begins with all the characteristics of Hodgkin's disease, and ends as a typical tuberculous lymphadenitis.

In about 20 per cent of the cases of Hodgkin's disease tuberculous changes are found somewhere in the body, and in about 10 to 12 per cent, tubercle bacilli are present in the affected lymph glands (Ziegler). Among 191 cases studied by Lemon there was clinical evidence of tuberculosis in only eight; while in the same number of unselected cases, seventeen showed signs of tuberculosis. Ewing (1919) remarks that "tuberculosis follows Hodgkin's disease like a shadow"; and that "tuberculous stigmata, or tuberculous family history, or tuberculous lesions in the body are the rule." But Ziegler found that a family history of tuberculosis was not a factor in forty-five of fifty-four cases which he investigated. The histologic changes characteristic of Hodgkin's disease and typical tuberculosis may occur in the same lymph gland. Sometimes the two processes are more or less blended (Crowder); or there may be a sharp line of demarcation between them (Benda, Wulffius). A case recently examined by me was that of a young woman who two years and one year before death had enlarged glands removed from her neck. These showed a typical histologic picture of Hodgkin's disease, and two guinea-pigs inoculated on each occasion with the diseased glands failed to develop tuberculosis. Postmortem examination about one year after the last removal of glands revealed an extensive tuberculosis of the lymph glands, most marked below the diaphragm, with tabes mesenterica. On microscopic examination, some of the lymph glands showed uncomplicated Hodgkin's disease; others showed typical tuberculosis only; while still others revealed both processes, usually well demarcated; but sometimes the tuberculous process appeared to be encroaching on and destroying the granulation tissue of the Hodgkin's disease. In a case of phthisis, Ewing (1919) found "in three small adjoining bronchial lymph glands, miliary tubucles in one, diffuse lymphocytes in another, and typical Hodgkin's granuloma in the third."

The inoculation of guinea-pigs with glands of Hodgkin's disease and which showed no microscopic evidence of tuberculosis has given varying results. Sternberg (1898), Hirschfeld (1912), Sisto, Lichtenstein (1921) and others have thus produced typical tuberculosis in the inoculated animals. Lichtenstein (1921) observed that guinea-pigs receiving injections with "pure" Hodgkin's glands lived three or more months, that is, they developed the disease slowly. Ewing (1919) has seen tuberculosis develop in similarly inoculated guinea-pigs after a period of from nine months to a year. On the other hand, Reed (1902), Simmons (1903), Longcope (1908), Askanazy (1912), Blumberg and others were unable to produce either tuberculosis or Hodgkin's disease in guinea-pigs inoculated with pure Hodgkin's glands. Blumberg's animals

died of "marasmus" without lesions of lymph glands. Negative results in monkeys were also reported by Longcope (1908), Askanazy (1912), Cunningham and McAlpin, Stewart and Dobson, and others.

Production of Hodgkin's disease in laboratory animals has been reported as a result of inoculation with Hodgkin's glands and with cultures of tubercle bacilli. Delbet claimed to have produced the disease in a dog, but his work was not repeated, and his report is not thoroughly convincing. Benda, Sticker and Löwenstein, Schaeffer, Sisto, and Lichtenstein (1910, 1921), after inoculating guinea-pigs with Hodgkin's glands, reported swelling of the lymph glands with characteristic histologic changes in these structures as well as in the liver and spleen. However, when a second animal was inoculated with the Hodgkin-like tissues of the first, the second pig developed tuberculosis and not Hodgkin's disease (Sticker and Löwenstein, and others). Herxheimer, Baumgarten, and others think that the human type of tubercle bacillus is responsible for Hodgkin's disease; a few others (Sticker) have considered the bovine type as the cause of the disease. Those who have defended the tuberculous etiology of Hodgkin's disease assert either that the strain of tubercle bacillus which causes it is not the ordinary form, or that there is some biologic peculiarity in the patient that gives rise to a response on the part of the infected lymph glands unlike that which is ordinarily induced by tubercle bacilli. It is either an attenuated strain (Sternberg, 1898; Lichtenstein, 1921) or a mutant form, a type peculiar to itself (Herxheimer, 1914). It is difficult to conceive how an attenuated strain of tubercle bacillus could cause so uniformly a fatal malady like Hodgkin's disease, while infections of other organs of the body with ordinary strains often run a chronic course.

The results of tuberculin tests have not confirmed the tuberculous nature of Hodgkin's disease. In most cases (Reed, 1902; Lehndorf, Simmons, 1903; Blumberg, Steiger, 1915) both the subcutaneous and the Pirquet test have proved negative.

In view of the mass of conflicting evidence, it is difficult to determine the true relation of tuberculosis to Hodgkin's disease. Sternberg (1909) admitted that he had probably gone too far in insisting that all cases of Hodgkin's disease were of tuberculous origin. But in 1925 he refers to "recent investigations which strengthen the original hypothesis of a peculiar form of tuberculosis" (Lichtenstein, 1921; Fraenkel and Much, 1923; and Kawatsure, 1925). Meyer and Meyer cite a case of Hodgkin's disease terminating in acute miliary tuberculosis in which the only discoverable source of the generalization of the infection was the rupture of a mass of Hodgkin's glands into a blood vessel. Fraenkel and Much (1923) have concluded that the granular rods which they described (1910) in Hodgkin glands are really a modified form of tubercle bacilli. They differ from ordinary tubercle bacilli in being

easily killed by antiformin and in being non-acid-fast. Their virulence is increased by the simultaneous injection of lactic acid. The fact that these "modified tubercle bacilli" are found in very small numbers in the affected glands is not an argument, they say, against the tuberculous nature of Hodgkin's disease, because tubercle bacilli are also few in number in other rare forms of tuberculosis, such as lupus vulgaris. Neither, they insist, does failure to reproduce characteristic Hodgkin's disease in experimental animals prevent one from accepting the view of its tuberculous nature, for typical typhoid lesions have not been produced in laboratory animals by inoculation with B. typhosus. Näslund thought that the chief factor in the production of the peculiar histologic characteristics of Hodgkin's disease was the "reaction-capacity" of the organism to the toxin of the tubercle bacilli.

Attempts have been made to explain the presence of tubercle bacilli in Hodgkin's disease on other grounds. Hirschfeld (1923) has suggested that a facultative symbiosis develops between tubercle bacilli and the unknown agent responsible for Hodgkin's disease. Gilbert and Weil and Weber (1908) thought that Hodgkin's glands furnished a favorable site for the lodgment and growth of tubercle bacilli. Spencer had suggested this possibility for diseased glands of different varieties and had observed the development of tuberculosis in a lymph gland which was the seat of metastatic carcinoma. Many students of Hodgkin's disease from Reed (1902) and Longcope (1903) to Lemon (1924) have considered the tubercle bacilli as secondary invaders only.

From the available data the conclusion is warranted that while tuberculosis of lymph glands and Hodgkin's disease have certain characteristics in common, and while tubercle bacilli are frequently found in Hodgkin's glands, it has not been proved that the tubercle bacillus is the essential etiologic factor in Hodgkin's disease. And yet recent work such as that of Lichtenstein (1921) and Fraenkel and Much (1923) has greatly strengthened the case for the tuberculous origin of the disease.

A new impetus was given to the study of the etiology of Hodgkin's disease when, in 1910, Fraenkel and Much described in these glands certain granular rods which were antiformin-fast and gram-positive but not acid-fast. They at first considered these structures as "related to but not identical with the tubercle bacillus." Kusonoki found these organisms in sixteen cases of Hodgkin's disease, and concluded that they were least numerous in those glands with the most marked fibrosis; they occurred in greatest numbers in those in which giant cells were most numerous; and that their presence was not related to the number of eosinophils.

As long as these granular rods could be studied only in sections and stained smears of antiformin digests of diseased glands, little could be

learned of their nature. There is little to be gained in merely citing the number of authors who found or did not find the granular rods. Views of their significance have taken two directions: (1) In their last contribution Fraenkel and Much (1923) have concluded that these rods are tubercle bacilli and that Hodgkin's disease is therefore a peculiar form of tuberculosis. Lichtenstein (1921) supports this view and contends that in the lymph glands tubercle bacilli are robbed of their acid-fastness by the action of lipase of the lymphocytes, and that they are either killed or have their aggressiveness reduced by the alleged bactericidal action of the lymphoid cells. This change in the biology of the tubercle bacillus in the lymph glands accounts for the atypical histologic picture of Hodgkin's disease. This contention was based on Bergel's view of the function of lymphocytes, a view which was not confirmed by Reed (1923). Simonds (1918) found less lipase in the spleen than in the liver and kidneys.

Other investigators have considered the granular rods of Fraenkel and Much (1910 and 1918) as identical with the diphtheroid bacilli first cultivated from Hodgkin's disease by de Negri and Mieremet. These are pleomorphic bacilli which, in cultures, show granular, banded, clubbed, branched and coccal forms. Bunting and Yates (1913) gave to this organism the name of *Bacillus hodgkini*. Fox studied eleven cultures of this micro-organism and found no uniformity in biology or morphology among different strains. Eberson outlined nine distinct groups of diphtheroids. He was unable to differentiate those isolated from Hodgkin's disease from numerous saprophytic diphtheroids.

This bacillus has been cultivated from the glands in Hodgkin's disease either in pure culture or associated with some other organism by Bunting and Yates (1913), Billings and Rosenow, Eberson, Rhea, Grumbach and others. Bunting (1915) isolated *B. hodgkini* from "every unrayed case" of Hodgkin's disease examined; and obtained it twice from the same patient. Bunting and Yates (1917) isolated it seven times from the same patient over a period of five years.

But it has also been found in other pathologic conditions: by Billings and Rosenow, in lymphosarcoma, and the enlarged glands of arthritis deformans; by Bunting (1915), in lymphosarcoma, arthritis deformans with lymph gland enlargement, and in the spleen in Banti's disease; by Fox, in metastatic carcinoma and glands regional to arthritis deformans; and by Harris and Wade, in tuberculosis, leprosy, blastomycosis, tertiary syphilis and tumors of various types. Cunningham studied the possibility of diphtheroids as accidental contaminations. Cultures were taken under ordinary aseptic precautions in six cases of enlarged glands with various lesions (one Hodgkin's), and all yielded diphtheroid bacilli. In six similar cases (two Hodgkin's), extraordinary care was taken to prevent contamination, and all cultures remained

sterile. During the period of these experiments, diphtheroid bacilli were found "several times" in 225 cultures made in the wards and operating rooms. Cunningham and Harris and Wade believe that diphtheroid bacilli are common and are widely distributed, and are sceptical concerning their etiologic significance in Hodgkin's disease.

Attempts to produce Hodgkin's disease in lower animals by inoculations with *B. hodgkini* or related diphtheroids have not been uniformly successful. Bunting (1914, 1915), Yates and Bunting (1915), Bunting and Yates (1917) report the production of histologically typical Hodgkin's disease in white rats, rabbits and monkeys by the injection of pure cultures of *B. hodgkini,* which, they claim, shows a specific affinity for lymphoid tissue. In addition to typical lesions the monkeys showed the characteristic blood picture. Grumbach induced lesions in guinea-pigs with cultures of diphtheroid bacilli isolated from glands in Hodgkin's disease; but his photomicrographs are not convincing evidence that he had produced true Hodgkin's disease. Mellon (1915), on the other hand, found this organism nonpathogenic for guinea-pigs; and rabbits into which it was injected became emaciated and died in five months without developing any characteristic lesions. Olitsky was unable to produce the disease in rabbits, and Rhea and Torrey were unsuccessful in monkeys.

Bunting and Yates (1915, 1917) gave repeated subcutaneous injections of killed cultures of *B. hodgkini* to a healthy man. He developed the blood picture which they had found to be characteristic of Hodgkin's disease—moderate leukocytosis, with relative and absolute increase in the number of mononuclears.

Kristjanson, using a watery extract of *B. hodgkini* as antigen, obtained complement fixation in three of sixteen cases of Hodgkin's disease. Olitsky, Moore, and Eberson obtained uniformly negative reactions. Moore, Olitsky and Kristjanson produced strong complement-fixing serums by immunizing animals to *B. hodgkini.*

The employment of autogenous vaccines in the treatment of Hodgkin's disease has not been successful in permanently curing the disease (Billings and Rosenow; Bunting, 1915; Fox, Mellon, 1915; Bunting and Yates, 1917).

In view of these conflicting reports, it is evident that the question of the identity of the exciting cause of Hodgkin's disease is still an open one. Benda has suggested that there may by no unitary etiologic factor. Many others look on this malady as due to some unknown virus which, when discovered, will be found to be specific. Kuczynski and Hauck express the belief that the giant cells contain the virus, which they place biologically between the tubercle bacillus and actinomyces.

Only two cases of probable transmission of Hodgkin's disease to man appear to have been recorded. Obratzow reported the case of a labora-

tory assistant who developed the disease soon after having examined the urine and feces and helping to plug the nose of a patient with the disease. Sisto tells of a surgeon who, while removing a mass of Hodgkin's glands, scratched his finger. Shortly thereafter he developed the disease, which began in the epitrochlear and axillary glands on the same side as the injury. But even in Sisto's case the possibility of coincidence cannot be forgotten.

PORTALS OF ENTRY

Little is definitely known of the means and routes by which the virus of Hodgkin's disease enters the body. Various difficulties interfere with the satisfactory detection of the point of origin of the disease. It may be extensive before it is discovered; it is not always possible to determine the oldest lesion by histologic examination; the virus may pass through the portal of entry without leaving a trace; and different glands in the same group usually show different stages of the disease. Ziegler mentions various possibilities as to portals of entry. Terplan has suggested that the region of the mouth is the portal of entry for the cervical glands, the respiratory tract for the peribronchial and mediastinal glands and the gastro-intestinal tract for the intra-abdominal glands. Billings and Rosenow and Bunting and Yates (1915) isolated *B. hodgkini* from diseased teeth or from the nose or nasal secretions and sinuses, and looked on these locations as possible portals of entry. Desjardins and Ford were impressed with the frequency with which Hodgkin's disease was associated with or had a definite relation to common chronic lesions about the mouth, such as bad teeth, diseased tonsils, and nasopharyngeal infections. But they remarked that "unfortunately in many cases the information available was not sufficiently explicit to warrant definite conclusions." Fraenkel and Much (1910, 1918), Meyer, Yates and Bunting (1915) and Terplan have reported cases in which the infection apparently entered through the lungs or bronchi; and Eberstadt, Weinberg, Schlagenhaufer, Terplan and others, cases in which the intestinal tract was the probable portal of entry. In the cases of Clarke (1901), Hauck, Hendricks, Sisto, and Kren, the infectious agent may have entered through a wound in the skin. Symmers (1924), however, insists that the portal of entry is never through the skin, but probably only through the mucous membrane, especially that of the gastro-intestinal tract.

PATHOLOGIC ANATOMY OF HODGKIN'S DISEASE

Hodgkin's disease is primarily an affection of the lymph glands. Usually beginning in one group, it ultimately involves all or nearly all of the lymphadenoid tissue of the body. It is usually accompanied by the formation of granulomatous masses in the viscera, and by anemia and cachexia. Acute and chronic forms occur.

According to most observers the cervical glands are most frequently affected. Lemon and Doyle and Desjardins and Ford have tabulated the percentage involvement of the various groups of glands.

Lemon and Doyle state that in their cases the disease did not always begin in the cervical glands. From the table it appears that the superficial glands are more frequently affected than the deeper groups. But in some cases the enlargement is limited to the internal glands (Meyer, Whittington, and Ziegler's larval form of the disease). Symmers (1924), however, found the abdominal and thoracic glands involved ten times as frequently as the cervical, and in four of his cases the latter group was not enlarged at all. Reed (1902) appeared to think that cases which did not begin in the cervical glands were doubtful.

Symmers (1924) has made an interesting distinction between two types of lymphoid tissue. The brunt of the attack in Hodgkin's disease is borne by the lymph glands of the abdomen, thorax, neck, axillae and groins, and by the auxiliary system of lymphoid tissue, including the

Percentage Involvement of Various Glands

Lymph Glands.	Lemon and Doyle.	Desjardins and Ford.
Cervical	100	96.3
Supraclavicular	58	....
Axillary	50	59.4
Inguinal	42	36.5
Abdominal	19	11.8
Mediastinal	..	33.3

liver, spleen and other residuary lymphoid collections in various parts of the body; while the vast array of lymphoid follicles which lie in the submucosa of the gastro-intestinal and urinary tracts practically always escape intact. From this, he says, it is apparent that the provocative agent in Hodgkin's disease has a selective action on certain groups of lymphoid tissue. This characteristic, Symmers emphasizes, Hodgkin's disease has in common with lymphatic leukemia, which also spares the lymphoid follicles of the gastro-intestinal tract. The same might also be said of tuberculosis of the lymphadenoid tissue; for tuberculous ulcers of the intestines rarely involve the Peyer's patches or the solitary follicles.

The extension of the disease from the primary focus is usually by way of the lymph stream to the next group of glands in the course of the flow of lymph. But in the generalization of the disease, which may occur with great rapidity, when practically all of the lymph glands of the body become affected, it is often impossible to trace the course of the infection. Weber (1917) regards the dissemination of the disease,

especially in the acute form, as a "septicemia of Hodgkin's disease." According to this view the nodules in the viscera are not metastatic growths as in carcinoma, but are due to metastasis or generalization of the exciting cause. Symmer's (1924) conception of Hodgkin's disease as an affection of the hemolytopoietic apparatus in which the lymph glands, in pursuit of their function as filters, arrest cells which have been discharged from the bone marrow, obviates the difficulty of accounting for the spread of the disease from one group of glands to another. And yet he asserts that involvement of the axillary glands is sequential to cervical and thoracic enlargements; and that inguinal involvement is sequential to swelling of the intra-abdominal glands.

The size of the several glands in each group varies greatly, partly because all of them are not involved simultaneously, and partly because in the later stages of the disease the increasing fibrosis results in a diminution in size. Because of the increasing fibrosis, the consistency of the individual glands varies; some are hard, others soft.

In most cases the glands are discrete, and not adherent to each other nor to the surrounding structures. But in a considerable proportion of cases the capsules become infiltrated, and the surrounding tissue may be extensively invaded. Sometimes the infiltrating cells are seen lying in rows between the layers of the capsule (Chiari, 1911). Gibbons insists that in most cases the capsule becomes invaded, first with lymphocytes, and then with nodules showing the typical granulomatous structure. In some cases the invasiveness is so marked that a sarcomatous transformation has to be considered (Gibbons; Dietrich, 1908; Hecker and Fischer; Lyon). The most markedly invasive type occurs in the mediastinum; less frequently, in the neck. In Lyon's cases the mass even eroded the sternum and ulcerated on the front of the chest.

The cut surfaces of the enlarged glands may be uniformly yellowish white or grayish white; or there may be visible narrow bands of fibrous tissue dividing the surface into lobules or nodules; or there may be small areas of brownish coloration resulting from previous hemorrhage, or light yellowish-brown patches which Aschoff thought were due to accumulations of eosinophils. In some glands small, irregularly shaped, "map-like" areas of necrosis are seen. These areas are not so numerous nor so prominent as in tuberculous lymphadenitis. They are due either to the direct action of toxic substances produced by the infectious agent (Sternberg, 1898; Lichtenstein, 1921), or to secondary infection (Yates and Bunting, 1915), or to interference with nutrition as a result of involvement of the blood vessels by the granulomatous process (Hauck, Tsunoda, and others). Pitt, and Andrewes (1901) felt doubtful as to whether necrosis occurred in uncomplicated Hodgkin's disease, and thought its presence indicated an added tuberculosis.

The tonsils are rarely involved in Hodgkin's disease. Ziegler found them swollen in three of fifty-four cases. Westphal thought that they were frequently the starting point of the disease, and occasionally found them swollen. Dutoit found the tonsils affected in a case in which the eyelids were also involved. Yates and Bunting (1915) have seen the microscopic picture of Hodgkin's disease in tonsils that were not grossly affected.

The most extensively invasive cases of Hodgkin's disease have occurred in the mediastinum and have been thought by many to have originated from the thymus. These growths invade the surrounding organs and tissues and may present in this respect all the vigor of a malignant tumor. Cases of this kind have been reported by Yamasaki, Gibbons, Beitzke, Welch, Karsner, Symmers (1911), Chiari (1911), Yates and Bunting (1915), Lyon, Hecker and Fischer and Symmers (1924). The author has recently observed such a case in which the histologic picture was typical of Hodgkin's disease with an extraordinary number of eosinophils which were present in all parts of the growth even in the most invasive portion. Ewing (1916), however, has recently reconsidered this question and has again gone over sections of such a case, reported by Symmers in 1911 as Hodgkin's disease of the mediastinum. In this case Ewing found all the features of a thymoma, including Hassall's corpuscles, polyhedral reticulum cells and "myeloid giant cells." Ewing concluded that the invasive form of mediastinal Hodgkin's disease is in reality a thymic tumor which should be separated from other forms of this disease, and which owes its malignancy to its origin from peculiar reticulum cells of the thymus.

The spleen was found to be involved in 78 of 100 cases by Murray. In the series of cases of Desjardins and Ford the spleen was clinically enlarged in 14.9 per cent. Symmers (1924) found the spleen increased in size in 65 per cent of his cases, most of which came to necropsy. In eight of his cases the average weight was 652 Gm. above the normal. In 50 per cent the spleen was nodular, but in most of them the nodules were not palpable on the surface.

On the surfaces made by sectioning the spleen it presents a characteristic appearance. Numerous sharply circumscribed, irregularly shaped, yellowish-white to grayish-white areas stand out distinctly against the dark red background of the pulp. Occasionally some of these masses are so large that they suggest metastatic sarcoma (O. Meyer). Benda, Warnecke and others have compared the appearance to "red porphyry," Janz to "Bauernwurst" and Spencer to "hardbake" (a kind of cake containing almonds).

The enlargement of the spleen is usually accompanied by involvement of the adjacent lymph glands. But Symmers (1909) thinks that there is a primary splenic form of Hodgkin's disease, and he and L'Esperance

have each reported a case. Ewing (1919) cites a case reported by Doncaster as probably genuine. The cases of Wade and Dowd are not so well authenticated, because the spleen was removed at surgical operation and the remainder of the body could not be explored. Ziegler admits the possibility of a primary splenic form of Hodgkin's disease, and discusses the difficulties in accounting for its pathogenesis.

In about 60 per cent of the cases of Hodgkin's disease, the liver is enlarged (Ziegler), and its surface is sometimes roughened with nodular elevations. On surfaces made by sectioning, numerous nodules of varying size are seen, usually small, occasionally quite large (Novak). They resemble in general appearance those in the spleen, and occur in the periportal connective tissue and sometimes extend into and replace the parenchyma. In three of Gibbon's and in Tsunoda's cases these masses had invaded the portal vein and protruded into its lumen. Steiger (1915) considers these nodules in the liver, not as metastases, but as "coordinate, autochthonous, inflammatory proliferations developing in preformed lymphoid tissue." Usually the liver and spleen are both involved; rarely, the liver alone (Yamasaki). Symmers (1924) has described a new and rare type of Hodgkin's disease characterized by massive involvement of the liver due to structural changes in the walls of the portal vein comparable to those in the lymph glands.

In Stahr and Synwoldt's case the common and cystic ducts were invaded by direct growth from the adjacent diseased lymph glands. Brauneck, MacCallum, Meyer (case 4), Peiser and Pepper have observed cases in which jaundice occurred, apparently as a result of pressure on the common duct by massive lymph glands.

Hodgkin's disease of the gastro-intestinal tract occurs in two forms: (1) those cases in which the lesions are almost entirely limited to the stomach and intestines (Eberstadt, Reimann, Schlagenhaufer's case 1, Partsch, McAlpin and v. Glahn); and (2) those in which the gastro-intestinal lesions are a part of a more generalized disease (Sternberg's [1898] case 6, Ziegler's case 6, Warfield and Kristjanson, Weinberg, Hauck, Schlagenhaufer's cases 2 and 3, Lichtensteins [1921] case 13, Satta, Terplan, Grossmann and Schlemmer, Terplan and Wallesch, and Lange). The cases of LaRoy, Castara and Georgantas, de Groot, and de Josselin de Jong are somewhat doubtful.

The lesions are usually limited to the stomach and upper part of the small intestine, but they may occur in the colon. They consist of massive thickening of the mucosa with or without extension into other coats. These nodular thickenings tend to undergo superficial necrosis and ulceration. The ulcers are of irregular shape, with firm, elevated edges, and bases that are either clean or covered with granular material. No tubercles are seen either in the floors of the ulcers or in the peritoneum opposite.

In one of Terplan's cases there was an ulcer at the base of the tongue which showed the histologic structure of Hodgkin's disease.

A terminal peritonitis is not uncommon (Warfield and Kristjanson, Hauck, Terplan, Lange, and others). The peritoneum itself was involved in the cases of Ness and Teacher, Fraenkel and Much (1910), and McAlpin and von Glahn.

Gibbons, LaRoy, MacCallum, Meyer (case 4), Hecker and Fischer, Sloboziano, Lyon, and Lubarsch have reported lesions in the pancreas. Usually there was one or more nodules. In Lubarsch's case the pancreas was markedly involved "much as the lacrymal and salivary glands in Mikulicz's disease."

Lesions in the lungs usually result from the extension of the disease from the peribronchial lymph glands. The invasion occurs either as a solid massive growth into the hilus of the lung giving a lobulated shadow in roentgenograms (Whitaker); or it extends for varying distances into the lungs as white radiating bands following the interlobular lymphatics, as in a case recently studied by the author. More rarely, isolated nodules, usually small, may be scattered through the lungs. The lung tissue may be replaced by the growth (Schottelius, Chiari, 1911); or the alveoli are filled with granulomatous material (MacCallum). In some instances the trachea (MacCallum, Ness and Teacher, Fraenkel and Much [1910, 1918], Koch) or the bronchi (Fraenkel and Much [1910], O. Meyer, Steiger [1915]) are eroded and perforated by the growth. Stenosis of the bronchi may result from pressure by the tumor mass (Ziegler) or from the massive granulomatous growth from the mucosa (Ferrari and Cominotti).

Gibbons was convinced that the nodules in the lungs did not develop in preexisting lymphoid tissue, but progressed as "a true malignant tumor metastasis, pushing the tumor already formed into the lung tissue."

In one of Terplan's cases there was an isolated nodule, which he considered the primary focus of the disease, in the apex of the right lung. The peribronchial and mediastinal glands were involved, more markedly on the right side.

Reckzeh, Yates and Bunting (1915), Hecker and Fischer, and Symmers (1924) have observed Hodgkin's disease of the pleura. In one of Symmer's cases it was massive. In about 20 per cent of cases pleural effusion occurs (Ziegler, Waetzold, MacCallum, Fabian [1909], McAlpin and von Glahn). In the cases of Edsall, Weber and Ledingham, and Gralka, the pleural fluid was milky. Ness and Teacher explained the occurrence of leaf-sided hydrothorax on the basis of compression of the azygos veins by the growing mass.

The heart and pericardium are usually not involved unless there is a massive growth in the mediastinum. Pericardial effusions may occur—hydropericardium (Yamasaki), hemorrhagic (Weber and Ledingham),

fibrinous (Brooks). Granulomatous nodules in the pericardium have been recorded by Reed (1902), Schur, Meyer, Yates and Bunting (1915), and others. The growth was beginning to invade the myocardium in the cases of Finlayson, Graetz, and Lyon. In a case of mediastinal Hodgkin's disease recently studied by the author the growth had replaced the greater part of the right auricle, and a finger-like mass hung into its cavity from the wall of the superior vena cava.

Invasion of vessel walls has been observed (Chiari, 1911a); of the aorta, by Hauck, Mueller, Fraenkel and Much (1923); of the vena cava by Fraenkel and Much (1923), Paunz, and the author; the jugular vein by Gibbons; the innominate vein by Steiger (1915); the intrahepatic branches of the portal vein by Gibbons and Tsunoda; and branches of the splenic vein by Longcope (1909).

Granulomatous deposits in the kidneys are usually found in the cortex (Gibbons, Koch, Galloway); and are almost always associated with Hodgkin's disease of the retroperitoneal lymph glands. Sometimes only one kidney is involved (Lyons). Occasionally the ureter is invaded (Schur, Paltauf [1897], Fraenkel and Much [1910]); rarely also the bladder (Fraenkel and Much [1910]).

The urine frequently gives a positive diazo reaction (Lehndorf, Hirschfeld [1912], Rosenthal, Glanzmann, and Urchs). Galloway has reported the presence of a Bence-Jones-like proteid in the urine of a patient with Hodgkin's disease with nodular involvement of the kidneys. No mention is made of the condition of the bone marrow.

Small granulomatous nodules have been found in the suprarenals by Yamasaki, Fraenkel and Much (1910), and Paunz; in the thyroid by Longcope (1903), Beitzke, and Ziegler (cases 6 and 8); in the testicle by Gulland, Murray, and Ziegler (case 6); and in the mammary gland by Kaufmann and the author.

The bones and bone marrow show lesions of the disease in a considerable proportion of cases. The frequency of their involvement cannot be accurately determined from the literature because of the infrequency with which these structures are explored at necropsy. Symmers (1924) thinks that the bone marrow is concerned in all cases. Hammar, in discussing a case which was probably Hodgkin's disease, although it was reported as "sarcomatous osteitis," suggests that the bone marrow may become involved before the lymph glands. Ziegler speaks of an osteoperiosteal form of Hodgkin's disease. Lesions of the vertebrae have been observed by Gibbons, Welch, von Müllern and Grossmann, Hauck, Simons (1918), Düring, Askanazy (1920), Mueller, Weber (1923a), Fraenkel and Much (1923); of the sternum, by Düring, and Lyon; of the skull by Beitzke; and of other bones by Beitzke, Hecher and Fischer, and Béclère.

Hodgkin's disease of the bones may take the form of granulomatous periostitis (Steiger [1915], Hecker and Fischer, Weber [1923a], and others), sometimes with the formation of osteophytes (Beitzke); or there may be rarefaction of the bone (Maresch), sometimes leading to pathologic fracture (Beitzke). When a lesion occurs in the periosteum of the posterior surfaces of the bodies of the vertebrae the spinal cord may be compressed (Düring, Weber [1923a], and others). Weber and Ledingham described a case of osteo-arthropathy of the extremities with irregular periosteal bone formation associated with mediastinal Hodgkin's disease.

The bone marrow shows lesions in from 30 to 40 per cent of the cases (Ziegler). Yellowish-white or grayish-white nodules of varying size, often not sharply demarcated, can be seen in the bone marrow, even in the shafts of the long bones where the marrow may be reddish to dark red (MacCallum). These nodules may be fibrogelatinous in consistency or may lead to the formation of cysts (Askanazy, 1920). Symmers (1917, 1924) described three types of changes in the marrow: (1) overgrowth of connective tissue with obliteration of the marrow cavity; (2) histologic changes essentially similar to those in the lymph glands; and (3) extraordinary hyperplastic changes in the marrow cells, especially the myelocytes and nongranular cells of the lymphocyte type.

Invasion of the skeletal muscles occurs in connection with the invasive type of Hodgkin's disease (Hecker and Fischer). Involvement of the following muscles has been specifically mentioned: cervical (Gibbons, Chiari); pectoral and intercostals (Yates and Bunting [1915], Henke, Symmers [1924]); muscles of the forearm and the psoas (Symmers, 1924).

Compression of the spinal cord resulting from granulomatous changes in the periosteum of the vertebrae has been mentioned. The brain is rarely involved. In Ziegler's case 12, the dura mater, pia mater and underlying brain substance showed lesions. One of Hecker and Fischer's patients suffered epileptiform attacks for a short time before death, and at necropsy a granulomatous nodule was found in the brain.

The skin is frequently involved in Hodgkin's disease—in about one third of Cole's cases, and in 9 per cent of those of Desjardins and Ford. Lesions of the skin occur in two forms: (1) miscellaneous, nonspecific lesions resulting from infection and toxemia without the characteristic histology of the disease, for example, pruritus, prurigo-like exanthems, urticaria, papillary efflorescences, toxic bullous erythema, bronzelike pigmentation, petechiae, edema (Bloch, Cole, Desjardins and Ford, Kren); or (2) more rarely, specific granulomatous infiltrations of the skin (Groscz, Arndt, Sibley, Hirschfeld [1917], Alderson, Doessikker, Fox, Langley, Grossmann and Schlemmer). In some cases

both types of lesions are found in the same patient (Arzt). Occasionally the specific lesions ulcerate, either with (Hirschfeld) or without (Alderson, Grossmann and Schlemmer) exposure to the roentgen ray.

HISTOPATHOLOGY OF HODGKIN'S DISEASE

Histologically, Hodgkin's disease is a diffuse granulomatous process, primary in lymphadenoid tissue, and characterized by a confused mixture of an extraordinary multiplicity of cell forms—small and large lymphocytes, endothelial and epithelioid cells, fibroblasts, mononuclear and multinuclear giant cells, and often eosinophils, polymorphonuclear neutrophils and plasma cells. It differs from the ordinary form of tuberculous lymphadenitis in that the latter is "patchy" in its distribution and is disseminated in discrete or confluent foci throughout the affected glands; while in Hodgkin's disease the lesions are more uniformly diffused through the glands (Andrewes, 1901). Walz has compared tuberculous lymphadenitis to Laennec's cirrhosis with its sharply demarcated interlobular connective tissue; and Hodgkin's disease to Hanot's cirrhosis with its diffuse intralobular increase of connective tissue.

In Hodgkin's disease all of the cells which compose the lymph gland proliferate; not always at the same rate, nor in the same degree at the same time. By this means a remarkable cellular composite results. Proliferation of one type of cell may outstrip the others (Gibbons). For this reason, the cellular variations observed at different stages of the disease are quantitative rather than qualitative, and cause no essential modification of the fundamental histologic character.

According to Reed (1902) and Simmons, the first change in Hodgkin's disease, i. e., the change in the smallest gland in an affected group, is a "proliferation of the flat, so-called endothelial cells which cover the reticulum of the lymph sinuses and of the large cells of the centers of the lymph nodes, which presumably are identical cells." But Longcope (1909), Fabian (1910), Lemon and Doyle, and Symmers (1911, 1917) thought that the initial change was a hyperplasia of the lymphoid cells with active proliferation in the germinal centers of the lymph follicles. Whatever the cell type that initiates the process, other cell forms soon begin to proliferate; the gland becomes temporarily more vascular; endothelial cells multiply; large and small lymphocytes, polymorphonuclear leukocytes and eosinophils, epithelioid and giant cells in varying proportions, fill the lymph sinuses; and the characteristic polymorphocellular granulation tissue results. Occasionally, at least in some glands, other cells may so far outstrip the giant cells and fibroblasts that the histologic structure becomes so cellular as to suggest sarcoma or leukemia (Bell). In the later stages of the disease, the connective tissue predominates, other types of cells diminish in number, and are found scattered irregularly, singly or in groups, in a dense fibrous stroma.

Fabian (1911) and Symmers (1911, 1917) recognize three stages in the development of the lesion in the lymph glands: (1) hyperplasia of the lymphoid elements; (2) formation of a polymorphocellular granulation tissue composed of epithelioid cells, mononuclear and multinuclear giant cells, fibroblasts and eosinophils, with occasional areas of necrosis; (3) hyaline fibrous induration, sometimes with such obscuring of the usual histology that the condition may be recognized only with difficulty. In any group of diseased glands, all stages may be seen in the different component units. Occasionally, different stages may be seen in the same gland (Longcope, 1909).

Ziegler distinguished three histologic types: (1) the most frequent, marked leukocytic infiltration (eosinophilic and neutrophilic) of a more or less fibrous granulation tissue; (2) granulation tissue without the leukocytic infiltration; and (3) a disputed form of simple lymphoid hyperplasia.

Invasion of the capsules of the glands may occur either in the form of lymphocytes lying in rows between the layers of the capsule (Chiari, 1911a), or the characteristic granulation tissue appears to break through the capsule and either forms nodules in the adjacent fat or invades the muscles and other contiguous structures. Dietrich (1908) has described a case in which the invasiveness was so marked that the lesion resembled "a lymphogranuloma-like sarcoma." The invading tissue does not differ from that in the affected lymph glands which do not show invasiveness, unless, as suggested by Meyer, there is a slight peculiarity in the giant cells in the infiltrating type.

The local invasiveness of Hodgkin's disease has been variously explained. Ziegler believed that the infectious agent spread through the capsule into the surrounding tissues and set up a reaction there similar to that in the lymph glands. Gibbons and others have looked on the invasion of the capsule and infiltration of adjacent structures as an indication of the malignant and neoplastic nature of the disease. In three of his cases Gibbons saw the tumor mass breaking through the capsule and forming a large mass on the outside, which in turn was walled-off by a secondary capsule. The capsule of a large gland may, therefore, not be the original capsule stretched out, but a composite capsule formed by secondary envelops which have grown to wall off outgrowths from the glands. Longcope (1909) looked on the formation of granulomatous nodules outside an affected gland as the result of a compensatory formation of new lymphoid tissue which itself in turn became diseased.

In Hodgkin's disease there appears to be an actual increase in the number of lymph glands in an affected group. Regeneration of lymphoid tissue does occur. Whether the newly formed lymph glands develop as

a result of growth of small masses of lymphoid tissue which Ribbert found to be widely distributed throughout the body, especially in the adventitia of the blood vessels, or whether they develop from sprouts or buds from the surfaces of lymph glands, as described by Vecchi, has not been clearly determined. Ritter did not believe that the new-formation of lymph glands was merely a substitution for an organ which had been destroyed, but that it depended on a definite stimulus, such as the presence of a tumor or an inflammatory process.

The giant cells which are so characteristic of Hodgkin's disease possess abundant cytoplasm and one or more round, oval, or irregularly shaped nuceli at or near the center of the cell, thus differing from the Langhans giant cell of tuberculosis. The nuclei of these cells are vesicular and show a distinct nucleolus. Karsner states that the multinuclear giant cells of tuberculosis, even when they resemble those of Hodgkin's disease, have pyknotic nuclei and are devoid of nucleoli. But Lubarsch (1923) noted giant cells in Hodgkin's disease whose nuclei were pyknotic and thought that this condition was the result of exposure to the roentgen ray. The cytoplasm of the giant cells show processes which unite them to other giant cells (Kusonoki), or to the stroma (Sternberg, 1898; Reed, 1902). The number of these cells varies in different cases, in different glands in the same case, and even in different parts of the same gland. They occur singly or in groups and clusters (Reed, 1902; Chiari, 1911; Kusonoki). In the late stages of the disease they are often seen lying in clefts in the dense fibrous tissue. Sternberg (1898), Reed (1902), Longcope (1903) and Gibbons, believed that the giant cells were derived from endothelium; Warnecke, Hirschfeld, Düring, and Symmers (1924) thought that they originate in the bone marrow and are filtered out by the lymph glands; Mallory has classed them as lymphoblasts. Sternberg (1898), Reed (1902), Longcope (1903) and others have observed occasional typical Langhans giant cells in Hodgkin's glands.

The lymphocytes in the affected glands gradually disappear so that in the late stages they are found in small islands or singly in the dense fibrous tissue. Plasma cells are frequently present in Hodgkin's glands (Reed, 1902; Longcope, 1903; Hirschfeld, 1912). They may be numerous (Kusonoki) or few in number (Mueller). They usually lie in the peripheral portions of the diseased gland in the connective tissue. Maresch, Vogt, Kusonoki and Frank have described cases in which plasma cells were so numerous that they designated the condition "plasma cell granuloma." All of these cases occurred in the cervical group of glands. In some of the cases (Maresch, for example) secondary nodules of similar histologic nature were present in the viscera.

The epithelioid cells are derived by practically all authors from the endothelium of the glands (Sternberg, 1898; Reed, 1902; Longcope,

1903). Symmers (1924), however, appears to consider many cells classed by others as epithelioid cells, as derived from the bone marrow, having been filtered out by the lymph glands.

The fibroblasts and connective tissue cells which form such a prominent part of the histologic picture in the later stages of the disease are derived by some from the connective tissue of the capsule, trabeculae and blood vessels; by others from the reticulum of the glands. Holler has considered Hodgkin's disease as an affection of the reticulo-endothelial system and would derive most of the characteristic cells of the lesions from this system. Letterer, and Schultz, Wermbter and Pulh, however, have presented evidence that this conception is incorrect. Cases differ in their tendency to fibrosis. Weis and Fraenkel have reported an instance in which this tendency was marked even in the lesions in the liver and spleen. Fibrosis is uncommon in the visceral lesions (Pitt).

Goldmann and Kanter noted that eosinophils were frequently numerous in enlarged glands which did not show tuberculosis, while in tuberculous lymphadenitis they were either absent, or present in very small numbers. They considered their presence of value in differential diagnosis. Reed (1902), Longcope (1903) and many others have noted the presence of eosinophils in Hodgkin's disease, sometimes in great numbers, as in the case of Kusonoki in which they predominated over other cells in places (also Graetz, and Warnecke). Andrewes (1901), Dietrich (1908), Longcope (1907) and others consider them of significance in differential diagnosis of Hodgkin's disease; but Karsner, Urchs and others do not think them of diagnostic importance because they are frequently found in lymph glands in other diseases, for example, in diphtheria (Foster). Perhaps Düring's view is a reasonable one to adopt, namely, that while eosinophils are not peculiar to Hodgkin's disease, there is no other condition in which they are found in such numbers.

Schridde stated that eosinophils tend to collect around areas of necrosis, sometimes forming a veritable phalanx. Kusonoki, and Lubarsch (1918) found them most numerous in the peripheral portions of the gland and in the connective tissue. Aschoff thought that compact groups of these cells might be responsible for the small areas of light brown sometimes seen on the cut surfaces of a Hodgkin's gland.

Klein emphasizes the occurrence of large numbers of eosinophils in affected lymph glands when Hodgkin's disease is complicated with toxic skin lesions, such as pruritus. The author recently studied a case in which there were enormous numbers of eosinophils in the lymph glands of a woman who suffered from an extremely irritating pruritus. Schlecht and Schwenker and Urchs think that the presence of eosinophils is an expression of a condition of anaphylaxis. Products of partial proteid decomposition originating in the areas of necrosis sensitize the

patient, and as a result of the local sensitization, the eosinophils are "enticed" into the affected glands. The itching lesions of the skin are placed on the same etiologic basis by Urchs.

Mueller has attempted to relate the number of eosinophils in the glands to the invasiveness of the lesions. In one of his cases these cells were numerous, and the disease was not of the invasive type; in another, they were few, and the lesions were extensively invasive. In my case mentioned above, the disease affected especially the mediastinal glands, and was extremely invasive. And yet, eosinophils were present in enormous numbers even in the mass that had grown through the wall of the superior vena cava and hung as a finger-like process into the right auricle.

There is general agreement that the eosinophils found in the glands are derived from the blood. Most of them are polymorphonuclear cells. Andrewes (1911) thought that they were modified polymorphonuclear neutrophils. But in many glands mononuclear eosinophils are seen. These may be eosinophilic myelocytes, as Symmers (1924) believes.

Charcot-Leyden crystals have been observed in fresh Hodgkin's glands (Ziegler, case 8). Düring thinks that they have some diagnostic significance, although they may occur in metastatic carcinoma of lymph glands. Their presence is apparently related to the eosinophils. Mayr and Moncorps found Charcot-Leyden crystals in suspensions of eosinophils isolated from the blood by a technic which they devised.

Areas of coagulation necrosis, usually small, are frequent, for example, in seven of Kusonoki's sixteen cases. Occasionally this process is limited to a single group of glands (Hirschfeld). Microscopically the necrosis of Hodgkin's disease differs from the caseation of tuberculosis in retaining the outlines of the dead tissue (Kraus and Lubarsch). Pitt doubted the occurrence of necrosis in uncomplicated Hodgkin's disease. Andrewes (1901) thought it indicated a superimposed tuberculosis; and Yates and Bunting, a secondary infection. Hauck, and Chiari (1911a) and Tsunoda found the cause in the localized interference with the circulation by the closure of blood vessels in the glands by their involvement in the granulomatous process. Bierich, Galloway, and Urchs suggested that resorption of partially disintegrated protein from these areas of necrosis may give rise to anaphylactic phenomena.

Sternberg (1898) stated that amyloid degeneration is common in Hodgkin's disease, and thought that it was due to infection with tubercle bacilli. But it has been found in uncomplicated as well as in complicated cases of Hodgkin's disease (Benda, two cases; Zuppinger; Bloch; Buchanan; Kaufmann; Paltauf, 1912; Steiger, 1915, in three of nine cases; Düring, Meyer; Schugt, and Schalong). The liver and spleen are most frequently affected; occasionally the kidneys and rarely the

suprarenals (Paltauf). Düring observed amyloid degeneration in the diseased glands themselves.

CHANGES IN THE BLOOD IN HODGKIN'S DISEASE

Anemia, usually of a secondary type, is a regular accompaniment of this disease. It may increase gradually in chronic cases or run a rapid course in the acute forms. Longcope (1909) mentioned a patient whose hemoglobin registered 22 per cent and whose red cells numbered 980,000.

Bunting (1911) noted a marked increase in size and number of blood platelets in all stages of the disease. But exhaustion of platelets may occur, due to the "eventual necrosis of the megalokaryocytes of the bone marrow." McAlpin was unable to confirm this increase in platelets by actual count.

In one fifth of the cases there is a normal leukocyte count or a leukopenia (Fabian, 1910). Fraenkel and Much (1910), Fabian (1910) and Weiss emphasize the polymorphonuclear leukocytosis, especially in the later stages of the disease. Desjardins and Ford found a leukocytosis of 11,000 or over in 46.2 per cent of their cases. Lincoln, Glanzmann, and Langley have reported very high leukocyte counts. (Glanzmann's case may have been a myelogenous leukemia.) In the early stages of the disease there may be a lymphocytosis; in the later stages, a lymphopenia, dependent on replacement of the lymphoid tissue of the glands by fibrous tissue. Bunting (1911) thought that the most striking feature of the leukocyte count was a high percentage of transitional leukocytes in all stages, due to the proliferation of the endothelial cells of the lymph glands. But McAlpin was unable to confirm this for any very large percentage of cases.

Leukopenia was observed by Gütig, Meyer, Mellon (1916) and Urchs. In Gütig's case the leukocyte count was 700; in Mellon's, 800. In one fourth of the cases there is an eosinophilia (Fabian, 1910). Pepper, Lincoln, Klein, Steiger (1913, 1915), Glanzmann, and Stewart have noted this condition. It was in the glands from Lincoln's case that Kofoid later found what he believed to be amebas. Steiger thought that increase in the eosinophils of the blood was associated with necrosis of the glands. Klein noted eosinophilia in those patients who suffered from pruritus and other skin lesions. Stewart found no relationship between the percentage of eosinophils in the blood and the number of these cells in the affected lymph glands.

Steiger (1913, 1915) considered the differential leukocyte count characteristic of the stage of the disease. In the first stage of lymphoid hyperplasia, there was lymphocytosis; in the second, or the stage of polymorphocellular granulation tissue, a neutrophilia; in the final stage

of fibrosis, a lymphopenia. It is doubtful whether such a rigid differentiation is often observed; because, while these histologic stages exist for the individual glands, all stages are to be found at the same time, even in the same group of glands. Bunting (1914) has stated that there is no single constant blood picture, but that in general two groups of cases can be differentiated: (*a*) those of a duration of one year or less, with a normal or slightly increased leukocyte count and a normal or slightly decreased percentage of polymorphonuclears; and (*b*) cases of more than one year's duration, with a sharp leukocytosis and a high percentage of polymorphonuclears; and throughout the disease an increase of transitional leukocytes and a gradual decrease in the lymphocytes.

Hemorrhages are not common accompaniments of Hodgkin's disease, but one of Bunting's (1911) patients suffered from hemorrhages from the mucous membranes, related possibly to the associated decrease in blood platelets; Ziegler's case 14 showed hematuria; Clarke's (1909) and Mellon's (1916) patients had serious epistaxis, which in Mellon's case was interpreted as vicarious menstruation; one of Weber's (1923b) patients had "recurrent purpura and hemorrhagic symptoms," and in seven of Westphal's cases there was "hemorrhagic diathesis, and in two, an outstanding hemophilia."

CLASSIFICATION OF HODGKIN'S DISEASE

Various attempts have been made to classify cases of Hodgkin's disease. The stages in its histologic development in the individual glands have been mentioned. Satta made the location of the process the basis of classification. Such a basis has the disadvantage that this is not a stationary disease, but a progressive involvement of the lymphoid tissue. Most cases are more or less chronic, that is, they last for a year or more; but acute cases occur, leading to death in a few months or weeks. Clarke (1901) found eleven acute cases in a series of forty-three. Moritz, Hirschfeld and Isaac, Beitzke, and Arrillaga have reported cases that proved fatal in about one month. It is always possible, however, that the disease may have been in existence for a longer time in the deeper, inaccessible glands. Perhaps it is more correct to say that these cases ran an acute course after the disease manifested itself clinically (Ziegler).

Symmers (1924) defines two groups of cases: (1) those in which the disease is confined to lymphoid structures; it may display itself in practically any organ in the body and still come in this group because minute collections of lymphoid cells are widely distributed—71 per cent of Symmer's cases; (2) those in which the changes are similar to those in group (1), but which in addition show a continuate infiltration and

destruction of adjacent structures (28 per cent of Symmer's cases). Looking at the disease from another point of view, Symmers (1924) makes five groups on clinical and anatomic grounds: (1) disease of regional lymph glands; predominant involvement of (*a*) abdominal glands (28 per cent), (*b*) abdominal and thoracic (43 per cent), (*c*) cervical glands (7 per cent); predominant involvement of (2) the thymus; (3) the spleen; (4) the liver; and (5) the (*a*) axillary glands, sequential to enlargements of the cervical and thoracic glands, and (*b*) inguinal glands, sequential to enlargement of the abdominal glands.

Yates and Bunting (1915) recognized three stages in the progress of the disease: (1) the stage in which the process is localized, the physical effects slight, and the physiologic effects almost unnoticed except on the blood picture; (2) the stage of considerable dissemination, physical effects more marked but still relatively slight, physiologic effects definitely developed (toxemia and anemia); and (3) the stage of widespread dissemination, physical effects pronounced (edema, dysphagia, etc.), and physiologic effects pronounced (anemia and cachexia).

Ziegler recognized broadly a localized and a generalized form of the disease. The former is frequently only a stage which precedes the latter. Based partly on localization of the lesions, Ziegler made a more elaborate classification into: (1) acute, (2) localized, (3) generalized, (4) mediastinal, (5) larval or typhoid, (6) splenomegalic, (7) osteoperiosteal, and (8) intestinal, forms. The mediastinal form is frequently very invasive. In the larval or typhoid form, the abdominal glands are chiefly involved, and the disease runs a course suggestive of typhoid fever. The other group names are self-explanatory.

HODGKIN'S DISEASE IN LOWER ANIMALS

Records of Hodgkin's disease in lower animals are chiefly either too brief and incomplete to be of value, or inaccessible. It will be possible, therefore, only to cite the reports on the animals concerned. The disease has been observed in the dog by Cadiac, Macfadyen, four cases, Paner, Yates (1908), Schreck, and Simons (1922); in the cat and horse by Cadiac; in the cow by Cadiac and du Toit; in the pig by Hodgson and Macfayden; in mice by Jobling and Simonds (1925). The animals mentioned have rarely been used in attempts to produce the disease experimentally. Delbet claimed to have produced it in a dog, but his experiment was not repeated. Schlagenhaufer inoculated a pig ("ein Eber") with an emulsion of Hodgkin's glands, but the animal remained well. Attempts to induce the disease in guinea-pigs, rabbits and monkeys have been discussed. No case of spontaneous Hodgkin's disease appears to have been observed in these common laboratory animals.

RELATION OF HODGKIN'S DISEASE TO OTHER DISEASES OF THE LYMPH GLANDS

Two questions remain for discussion: the relation of Hodgkin's disease to other diseases of the lymph glands, such as leukemia and lymphosarcoma; and the possibility of sarcomatous transformation of Hodgkin's disease.

At the beginning of this paper the steps were given by which the composite group of pathologic conditions described by Hodgkin has been broken up into a number of subgroups, each with a definite histopathology and a somewhat less characteristic clinical picture. There has been a tendency of late years to recombine these conditions into one group; Warthin (1923), for instance, thinks that Hodgkin's disease, aleukemia lymphosarcoma and lymphatic leukemia all have a genetic unity. Symmers (1924) points out certain parallelisms between Hodgkin's disease and myelogenous leukemia. Bunting (1915), after referring to the isolation of *B. hodgkini* from numerous other diseases of the lymph glands, such as lymphosarcoma and lymphatic leukemia, suggests that "there are organisms of the diphtheroid group of varied virulence, but with specific affinity for lymphoid tissue, including bone marrow, and that clinically and pathologically we have varied reactions to the different strains."

Since etiology is universally recognized as the logical basis for the classification of diseases, and since we do not yet know the exciting cause of any of these obscure lesions of lymphoid tissue, it seems best to adopt Ewing's (1923) view and maintain clear histopathologic distinctions between the different forms of lymph gland enlargements until we know their origins. It would seem that the work of discovering their etiologic factors would be furthered, or at least not hindered, by maintaining these distinctions. If a common etiologic factor is discovered, there will be little difficulty in combining them into one common group with, perhaps, subgroups to correspond to the now recognized different histopathologic forms. Such a method will emphasize the necessity of determining why the same etiologic agent induces one type of lesion in one case and another type in another case.

Although, as Bunting (1914) remarks, the cells in Hodgkin's glands are atypical, they show none of the antagonisms to other body cells which characterize a malignant tumor. And yet, not infrequently it is difficult to make a differential diagnosis between Hodgkin's disease and lymphosarcoma. Lymphosarcoma may contain more than one type of cell, but, in general, it is characterized by the simplicity of its cellular structure (Ghon and Roman), while Hodgkin's disease shows a remarkable multiplicity of cell types. This must always be the basis of differential diagnosis, even in those cases mentioned by Bell in which one type of cell so outgrows others as to make differential diagnosis difficult.

Sternberg, in discussing Beitzke's paper, stated his belief that Hodgkin's disease may be transformed into lymphosarcoma; and Warthin declared that he had seen such a thing occur. Mueller reported a case which was diagnosed Hodgkin's disease, and after several recurrences during a period of seven years, was finally classified as a lymphosarcoma. Levin (1919) stated that lymphosarcoma and Hodgkin's disease can be encountered in the same patient. He believed that lymphosarcoma differs from Hodgkin's disease in that in the former only one type of cell proliferates. Ewing (1923) had never seen Hodgkin's disease transformed into anything that he would call a lymphosarcoma. This disagreement is evidence of the complexity and difficulty of the problem. As there is no differential stain that will accurately distinguish between the different types of cells concerned, this difference of opinion will probably continue until the etiologic factor in these pathologic conditions has been discovered.

The invasiveness of certain cases of Hodgkin's disease has been the basis of the opinion expressed by Chiari (1911a), Karsner, Yamasaki, Yates and Bunting (1915) and others that Hodgkin's disease can be transformed into sarcoma; and for the opinion of Gibbons, Mallory Tsunoda and others that Hodgkin's disease is a type of sarcoma. In regard to invasiveness Symmers (1911) has suggested two possible interpretations: (1) The invasion either is due to sarcomatous transformation of the original granulation tissue, or it is an expression of compulsory growth and is locally malignant rather than due to the possession of autonomous properties by the cells; or (2) the occurrence of secondary nodules may signify neoplastic conversion of the original growth and transmission of cell emboli with autonomous qualities to distant organs; or the transplanted provocative agent may find a suitable field of activity in the form of preexisting lymphomatous foci which have become secondarily involved. But he declared that destructive infiltration and formation of secondary nodules in distant organs is highly presumptive evidence of malignancy, and neoplastic conversion is the simplest explanation.

But invasiveness has been observed in known granulomatous tissue. Thus, for example, Chiari (1911b) has described the invasion of the wall of the bronchus by tuberculous granulation tissue. Furthermore, as pointed out by Meyer, infiltrative growth in Hodgkin's disease is not related to any specific structure in the growing mass; certainly not to any anaplastic transformation of any specific cell form into a malignant tumor. In an extremely invasive case of Hodgkin's disease recently studied by the author, the tissue which had grown into the right auricle and vena cava still possessed all of the histologic characteristics of Hodgkin's disease even to the presence, thoroughly disseminated throughout the growth, of enormous numbers of eosinophils. It does not seem possible

to state, in the present condition of our knowledge, whether Hodgkin's disease does sometimes undergo sarcomatous change, or whether it may still retain its granulomatous nature and yet invade much as a malignant tumor. Ewing (1919) has used the term "Hodgkin's sarcoma" for these invasive forms.

Symmers (1924) has, in his newer conception of the nature of Hodgkin's disease, offered evidence of its essential relation to myelogenous leukemia. He suggests that these two diseases may represent different qualitative responses to the same type of provocative agent. Fabian (1911) points to the clinical and even the gross anatomic similarities between Hodgkin's disease and leukemia, but considers them wholly unlike microscopically. Warthin (1923) and others claim that Hodgkin's disease may be transformed into leukemia; Ewing (1923), and Motzfeld state that they have never seen this occur. Dr. A. W. Crane informs me that patients with Hodgkin's disease, after being vigorously treated with the roentgen ray, sometimes develop the blood picture of leukemia. The cases of Lincoln, Glanzmann and Langley suggest this possibility, although in their cases the diagnosis of Hodgkin's disease was not perfectly clear. Dietrich has reported a curious and perplexing case in which a patient was treated for mixed cell leukemia. But lymph glands, spleen and liver obtained at necropsy three months later showed the histologic picture of Hodgkin's disease. Many Fraenkel-Much granular rods were found in the sections from this case. From this the possibility suggests itself that if Hodgkin's disease can be transformed into leukemia, the reaction may be a reversible one.

Ziegler considered mycosis fungoides as a type of Hodgkin's disease localized in the skin. Ceelen and Zurhelle have reported cases of mycosis fungoides with lesions in the viscera, and considered the disease as essentially an infectious granuloma. Arndt and Arzt thought the two conditions different. Berger has pointed out the similarities between them, but was convinced that they were separate and distinct diseases. The case of Pardee and Zeit supports this view.

There is a similar difference of opinion relative to the relationship between Hodgkin's disease and Mickulicz's disease (Külbs).

SUMMARY

Hodgkin's disease, in the sense in which the term is used in this review, is almost universally recognized as a histopathologic entity. But the fundamental problems of its nature and etiology are still unsolved. Recent work has again focused attention strongly on the tubercle bacillus as a possible etiologic factor. The progress thus far made in the study of diseases of the lymph glands has been the result of the splitting up of the composite group of pathologic conditions originally described by

Hodgkin, into leukemia, pseudoleukemia, lymphosarcoma and Hodgkin's disease. There is a tendency to recombine these diseases into a common group. Until their etiology is discovered, the final solution of the problem of their relation to each other will be furthered by rigidly maintaining the histopathologic criteria already devised for their differentiation.

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Notes and News

Aid Offered for Research.—The committee on scientific research of the American Medical Association invites applications for grants in aid of research on problems of interest to clinical medicine. Applications may be addressed to 535 N. Dearborn St., Chicago.

Superintendent Appointed for New Haven Hospital.—Dr. Albert W. Buck, of the Johns Hopkins Hospital, has been named superintendent of the New Haven Hospital, to succeed Dr. Willard C. Rappleye, who recently resigned to become chairman of the International Commission on Medical Education.

Grants for Research.—The National Tuberculosis Association has granted $3,000 to Esmond R. Long of the University of Chicago for continuation of his work on the nutrition of the tubercle bacillus.

The National Research Council through its committee on research in problems of sex has granted $10,300 to Frank R. Lillie and Carl R. Moore of the University of Chicago for support of work on the biology of sex.

Convention of American Society of Clinical Pathologists.—The Fifth Annual Convention of the American Society of Clinical Pathologists will be held in Dallas, Texas, April 15, 16 and 17, 1926, at the Baker Hotel.

A cordial invitation is extended to all clinical pathologists to attend the convention whether they are members or not.

Appointments by National Research Council.—At the meeting on Sept. 26, 1925, the Medical Fellowship Board of the National Research Council in Washington appointed the following new fellows: L. R. Cerecedo, Ph.D., in biochemistry; Rudolph Fisher, M.D., in bacteriology; R. W. Girard, M.D., Ph.D., in physiology; W. C. Hunter, M.D., in pathology; Barbara B. Stimson, M.D., in physiology; Jeffries Wyman, Jr., in physiology. At present the Medical Fellowship Board has 39 appointees distributed with respect to sciences, as follows: anatomy, 3; bacteriology, 6; biochemistry, 8; neuropathology, 1; pathology, 7; pharmacology, 3; physiology, 11.

Fellowships for Women.—The American Association of University Women announces fellowships which are open to American women, among which are the Sarah Berliner Research and Lecture Fellowship for women holding the degree of Ph.D. or D.Sc. The value of the fellowship is from $1,000 to $1,200, available for research in biology, chemistry or physics. The association also announces that the Alpha Xi Delta fraternity offers a fellowship of $1,000 for graduate work in the field of medicine or mental science available for the year 1926-1927; it will be awarded by the committee on fellowships of the American Association of University Women. The association offers a $1,200 fellowship to carry on research in some country other than the fellow's own during the academic year 1926-1927. The stipend will be paid half-yearly in advance, and the work can be done in any important university or institution. Applications should be made to the chairman on fellowships, Prof. Agnes L. Rogers, Bryn Mawr College, Bryn Mawr, Pa.

Four Pathologists at the German University in Prague.—In celebration of the sixtieth birthday of Anton Ghon, professor of pathology in Prague, Rudolf Fischl has published (*Med. klin.* **22**:39, 1926) interesting personal reminiscenses of four successive occupants of that chair, namely, Edwin Klebs, Hans Chiari, Richard Kretz and Anton Ghon.

In Memoriam.—In memory of Dr. Norman Lothian (British) and Dr. Darling (American), the two members of the Malaria Commission of the League of Nations who were killed in a motor accident near Beirut last May while investigating malaria condition in Syria, the League's Health Committee has decided to create a "Lothian Scholarship" and a "Darling Prize," which will be awarded periodically for the encouragement of malariological study.

Report of Foot-and-Mouth Disease Research Committee of England.—The first progress report of the Foot-and-Mouth Disease Research Committee, of England, is largely of a preliminary nature: researches and experiments include those on cattle, sheep and pigs, and arrangements for this class of inquiry have been completed. The extensive and well appointed buildings at Pirbright, Surrey, constructed and equipped as a cattle testing station, have been placed at the disposal of the committee by the Ministry of Agriculture and are admirably adapted for the purpose. The investigation will be of such a searching character as should lead to definite results, as far as present suggestions and theories can affect the situation.

Medical Fellowships.—The Committee on Medical Fellowships of Western Reserve Medical School, Cleveland, announces that two full-time research fellowships at $1,500 per annum will be available for the academic year 1926-1927. The period of service is not less than ten months, and promising Fellows may be reappointed a second year for $2,000. The appointments are open to properly qualified persons for research in any department of the medical school. Applications should contain brief statements as to previous research training and degrees, together with the nature and plan of work contemplated and letters of recommendation; they should be addressed to the Committee on Medical Fellowships, 2109-2115 Adelbert Road, Cleveland, before April 5.

Yale to Revise Educational Methods.—The faculty of Yale University School of Medicine, New Haven, is considering the abolition of the year system of study and the division of the student body into classes. Dean Winternitz has announced that plans are being made to revise thoroughly the educational methods with a view to placing less emphasis on routine class work and more on independent thought and research. The program will involve abolishing the system of examinations at the end of courses. The student will select the sequences of his studies in the first two years of the curriculum, and after qualifying for clinical subjects will again be allowed the liberty of choice. The completion of these studies and their arrangement will be largely a matter of his choice and ability, and his admission to courses will depend on his fitness as determined by the instructor in charge. As a check on the accomplishment of students, there will be group examinations and a graduating thesis, and within reasonable limits the student will determine when he will present himself for such a test.

Faculty and Other Appointments.—Dr. Thurman B. Rice has resigned his position as director of the Indiana State Hygienic Laboratory and returned to the department of pathology of the Indiana University School of Medicine as

associate professor of hygiene and sanitary science. His new position entails responsibility for the courses in medical bacteriology as well as those pertaining to public health.

Arthur W. Wright, M.D. (Harvard, 1923) has been appointed assistant professor in pathology in Vanderbilt University. Dr. Wright served as assistant to Dr. F. B. Mallory in the Boston City Hospital from 1923 to 1925.

The new medical building at Vanderbilt is situated on the campus and there is close physical continuity between the laboratories and the hospital. The department of pathology faces the open campus on two sides.

J. Ross Veal has been appointed instructor in pathology at the University of Alabama.

Ferdinand C. Helwig, instructor in pathology in the University of Kansas School of Medicine, was recently promoted to assistant professor.

Ellis W. Wilhelmy, who recently returned from a position as assistant resident in medicine at the Cleveland City Hospital, has been appointed assistant in pathology at St. Margaret's Hospital, Kansas City, Kansas, succeeding Dr. Emsley T. Johnson.

Emsley T. Johnson was recently appointed assistant pathologist in Research Hospital, Kansas City, Mo. F. C. Narr is the pathologist at Research Hospital, and director of the Diagnostic Clinic.

Mynie G. Peterman, associate in pediatrics, Mayo Clinic, Rochester, Minn., has accepted the position of director of laboratory and research at the Children's Hospital, Milwaukee.

At Tufts College Medical School, Dr. Frank H. Dunbar has been appointed assistant professor of pathology.

Abstracts from Current Literature

Pathologic Physiology

[The abstracts have been prepared by the physicians whose names are signed to them. Unsigned abstracts may be credited to the editorial staff.]

JAUNDICE AS AN EXPRESSION OF THE PHYSIOLOGICAL WASTAGE OF CORPUSCLES. PEYTON ROUS and D. R. DRURY, J. Exper. Med. **41**:601, 1925.

Biliary obstruction was produced in a series of dogs by cutting the common duct between ligatures. The cystic duct was also severed to rule out the influence of the gallbladder to delay jaundice. The hemoglobin percentage and bilirubin content of the blood and the bilirubin excretion in the urine were followed from day to day. Routine examinations of the urine for evidence of kidney injury showed at the most only the slightest disturbance, which is not uncommon in the first weeks of jaundice.

In two charts of typical findings in individual dogs the authors point out that after an initial period when the chloroform anesthesia provided a cause of complication, the changes in bilirubinemia corresponded notably in time and degree with similar variations in the hemoglobin percentage of the blood. The course of events found irregular expression in the output of bilirubin through the urine. Removal of a portion of the circulating blood pigment by bleeding resulted in a corresponding, or more than corresponding, reduction in bilirubinemia. With recovery from the anemia the bilirubinemia curve mounted with that of the hemoglobin.

The close correspondence in the changes in bilirubinemia with the changes in circulating hemoglobin, even when the tissue icterus is of long standing, in the opinion of the authors, indicates the presence of a barrier (the walls of the blood vessels) to the distribution of bile pigment from the blood. The influence of the barrier is evidenced by the relatively negligible amount of bile pigment in the lymph compared with that in the blood in the long jaundiced animal.

The authors further conclude that the jaundice that develops after obstruction of the common duct in the absence of complications expresses the physiologic wastage of corpuscles occurring from day to day; and the intensity of the bilirubinemia varies as does the total of functioning hemoglobin-containing tissue from which this wastage takes place.

UROBILIN PHYSIOLOGY AND PATHOLOGY. V. THE RELATION BETWEEN UROBILIN AND CONDITIONS INVOLVING INCREASED RED CELL DESTRUCTION. ROBERT ELMAN and PHILIP D. MCMASTER, J. Exper. Med. **42**:619, 1925.

Further evidence is presented, in addition to that of previous papers, that the intestinal tract is, under ordinary circumstances, the sole place of origin of urobilin. So long as the biliary tract remains sterile, the presence of the pigment in bile and urine is entirely dependent on the passage of bile to the intestine.

Animals rendered urobilin-free by the collection of all the bile from the intubated, uninfected common duct, remain urobilin-free during and after extensive blood destruction caused by intravenous injections of distilled water, as also after reinjections of the animal's own blood, hemolyzed in vitro. No urobilin appears in the bile, urine or feces of animals so intubated when blood

destruction has been caused by sodium oleate, or by an agent, toluylenediamine, which damages the liver as well as the blood.

On the other hand, when bile flow into the intestine is uninterupted, urobilinuria occurs during blood destruction caused in any of the ways mentioned, and it parallels, both in severity and duration, the destructive process.

Merely increasing the amount of bilirubin within the intestines of healthy dogs by feeding urobilin-free bile will lead to marked urobilinuria. The extravasation of blood into the tissues resulting from the trauma of an operation for intubation of a bile duct does not lead to urobilinuria in animals losing all of the bile after this operation, but may do so when only a small fraction of the bile is drained, while the remainder reaches the intestine as usual. The production of artificial hematomas, without operation, is not followed by urobilinuria, under the circumstances last mentioned, but merely by an increase in the bilirubin of the bile. The effect on the liver of the anesthetic employed during the intubation may be responsible for the difference in the two cases.

During the course of certain intercurrent infections affecting some of the intubated animals, notably distemper, there was a drop in the hemoglobin percentage of the circulating blood, accompanied by an increased output of bile pigment or further by urobilinuria, when the conditions were such that bile still reached the intestine. The findings pointed to increased blood destruction as a factor in the urobilinuria.

The evidence presented, taken with that of previous papers, suffices to demonstrate that urobilinuria, occurring during blood destruction, is primarily the result of an increased excretion of bilirubin, from which, in turn, an unusually large quantity of urobilin is formed within the intestine. The liver fails to remove from the portal blood all of the latter pigment, which is resorbed, and consequently some of it reaches the kidneys and urine.

The work has been carried out on animals with uninfected biliary tracts and livers, except in one case which has received special mention. The influence of infection of the biliary tract on the place of formation of urobilin and the development of urobilinuria will be discussed in a succeeding communication.

AUTHORS' SUMMARY.

THE PHYSIOLOGICAL RESPONSE OF THE CIRCULATORY SYSTEM TO EXPERIMENTAL ALTERATIONS. I. THE EFFECT OF INTRACARDIAC FISTULAE. EMILE HOLMAN and CLAUDE S. BECK, J. Exper. Med. **42**:661, 1925.

An abnormal communication, experimentally produced between the right and left ventricles, causes a deflection of part of the blood stream into the shorter pulmonary circuit. Proceeding pari passu with the increase in volume flow of blood through this shorter circuit, a gradual enlargement of the heart occurs limited to that part of the circulatory system through which the deflected blood passes; namely, the left ventricle, the right ventricle, the pulmonary artery and the left auricle. There is also a demonstrable hypertrophy of the right and left ventricles, which presumably is the result of the increased effort necessary to propel forward an increased volume flow of blood, since it cannot be attributed to an increased peripheral resistance.

Immediately after the production of the defect, the right auricle and aorta become smaller than usual, conforming in size to the decreased volume flow of blood through them. As full compensation for the deflected flow occurs by an increase in total blood volume, they return to their normal size. If full compensation has not occurred they remain smaller than normal (Dog XII).

The changes incident to the establishment of an opening in the septum are entirely dependent on the size of the defect, and hence, on the extent of the volume of blood deflected into the shorter circuit. Commensurate with the volume of blood deflected, there is a fall in general blood pressure. If the animal survives the immediate fall in blood pressure, certain compensatory adjustments occur which reestablish a more normal blood pressure: (*a*) an immediate increase in pulse rate; (*b*) a gradual increase in total blood mass. The increase in blood volume is directly commensurate with the size of the defect. The pulse returns to a normal rate when complete compensation through an increase in blood volume has been attained.

It is suggested that the enlargement of the heart seen clinically in so-called "idiopathic hypertrophy," "essential hypertension," and also in certain cases of cardiorenal disease, may be due to an increase in total blood mass following some interference with the mechanism for its control. The seat of this impairment in blood volume control may be: (*a*) in a chemical alteration in the blood, (*b*) in a diseased function of the kidneys which may be responsible for a decreased elimination or for a change in the chemical composition of the blood, or (*c*) in an abnormal stimulation of the organs producing the cellular elements of the blood.

AUTHORS' SUMMARY.

THE PHYSIOLOGICAL RESPONSE OF THE CIRCULATORY SYSTEM TO EXPERIMENTAL ALTERATIONS. II. THE EFFECT OF VARIATIONS IN TOTAL BLOOD VOLUME. CLAUDE S. BECK and EMILE HOLMAN, J. Exper. Med. **42**:681, 1925.

Alterations in the peripheral circulatory bed, either by the inhalation of amyl nitrite or by the intravenous injection of histamine, result in a marked reduction in the size of the heart, due, it is suggested, to a decrease in the volume of blood contained in the central circulatory bed incident to a dilatation of the peripheral bed. Gordon and Wells have observed similar variations in heart size in the rabbit, and suggested that they were intimately related to blood pressure and made no reference to changes in blood volume distribution. The variations in heart size could not be attributed merely to the altered rate of cardiac contraction, since there was no invariable interrelationship established.

Contraction of the peripheral vascular bed, either by the intravenous injection of epinephrin, or by an acute increase in the intracranial pressure, results in a demonstrable increase in the size of the heart, due, it is suggested, to an increase in the volume of blood contained in the central circulatory bed. Again, variations in the rate of cardiac contraction alone cannot be considered responsible for these variations in heart size.

The size of the heart is commensurate with the volume flow of blood through it, whether the latter is altered by massive blood letting, by massive transfusions, or by a redistribution of the normal blood volume.

AUTHORS' SUMMARY.

EXCRETION OF NEUTRAL RED INTO THE HUMAN STOMACH. A. WINKELSTEIN and J. M. MARCUS, J. A. M. A. **85**:1397, 1925.

With normal or subnormal free hydrochloric acid neutral red is excreted into the stomach in an average of twenty-one minutes. In hyperacidity, duodenal ulcer, or gallbladder disease the appearance of the dye may be hastened seventeen minutes, while in achylia gastrica excretion is greatly delayed, or the dye may fail to appear in the stomach.

MODIFIED PHYSIOLOGIC PROCESSES FOLLOWING TOTAL REMOVAL OF THE LIVER. FRANK C. MANN, J. A. M. A. **85**:1472, 1925.

The blood sugar decreases from the instant the liver is removed. Muscle glycogen decreases concomitantly. When the blood sugar falls to a certain level the characteristic symptoms associated with low blood sugar appear, and if glucose is not administered, the animal dies in a condition of hypoglycemia. The proper administration of glucose prevents the hypoglycemia and the development of the characteristic symptoms, and prolongs the life of the animal many hours until a different condition develops and the animal dies. The cause of death in the latter condition has not been determined. The action of glucose in the hypoglycemic condition is specific. The decrease in blood sugar following hepatectomy also occurs in the condition of hyperglycemia that follows extirpation of the pancreas. The transitory hyperglycemia that follows the administration of epinephrin, production of asphyxia and similar procedures does not occur after hepatectomy. An animal will die following the development of hypoglycemia with a considerable amount of glycogen still present in the muscles. If the blood sugar level is maintained above normal in the hepatectomized animal, muscle glycogen will increase. Urea formation ceases immediately after removal of the liver. The amino-acids, which normally would have entered into the process of urea formation, accumulate in the blood and, if the kidneys are active, are excreted in the urine. Uric acid is not destroyed, and it actually accumulates in the blood and tissues or is excreted in the urine if renal activity is maintained. A yellow pigment accumulates in the hepatectomized animal which gives a positive reaction to the accepted chemical tests for bilirubin as well as produces the same curve of light transmission, with the spectrophotometer, as bilirubin.

AUTHOR'S SUMMARY.

PATHOLOGIC PHYSIOLOGY OF LIVER IN RELATION TO INTOXICATION AND INFECTION. EUGENE L. OPIE, J. A. M. A. **85**:1533, 1925.

The liver by means of the peculiar endothelium of its sinusoids fixes insoluble inorganic particles, many kinds of organic particles, such as bacteria and substances in colloid suspension, and perhaps by the same means many substances dissolved in the plasma.

With immunization, the liver shows increased ability to fix bacteria and foreign proteins and to render them harmless.

The liver removes from the portal blood many injurious agents which enter from the gastro-intestinal tract, and prevents their entrance into the systemic circulation.

Fixation of injurious substances may cause destructive changes in the liver and permanent lesions of the organ.

AUTHORS' SUMMARY.

OBSERVATIONS ON THE BLOOD CELLS OF RABBITS AFTER SPLENECTOMY. R. HOWARD MOLE, J. Path. & Bact. **28**:637, 1925.

Mole performed complete or partial splenectomies on seventeen rabbits, and studied the effect produced on: (1) the number of erythrocytes, (2) the number of reticulated erythrocytes, (3) resistance of erythrocytes to hypotonic saline and saponin, (4) number of white cells. After the removal of the whole or half of the spleen an immediate decrease in red cells took place; in about a week they began to increase, and in two months were usually more numerous than before operation. The decrease was less marked, while the increase began

earlier and was greater after partial splenectomy. The reticulocytes increased during the first two weeks, suggesting homopoiesis. After two months these cells were less numerous than in the controls, probably due to lack of destruction in absence or reduction of the spleen. The increase in red cells two months after operation was accompanied by a slight increase in resistance to hypotonic saline; their resistance to saponin was unchanged. The number of white cells, chiefly leukocytes, was increased during the first week after partial or complete splenectomy.

ERNEST M. HALL.

PAROXYSMAL HEMOGLOBINURIA. J. ENNEKING, Nederlandsch Tijdschr. v. Geneesk. **2**:1515, 1925.

The special feature was a hemoclastic crisis preceding the attacks of hemoglobinuria in a man, aged 37. The autolysin had hemolytic action in the test tube even without chilling. The attacks of hemoglobinuria seemed to occur exclusively in the night. The man died from necrosis of the bowel.

THE ACTUAL STATE OF THE QUESTION OF TISSUE CULTURES. A. GRUMBACH, Rev. méd. de la Suisse Rom. **45**:537, 1925.

This review of the most important articles on tissue culture recalls the interesting suggestions concerning the influence of one kind of cell or its products on the growth of another, and the ensuing possibilities in neoplastic cellular relationships.

G. B. RHODES.

THE THYROID GLAND AND PULMONARY TUBERCULOSIS. K. GERNER, Trav. d'Inst. d'anat. path. d. Univ. de Pologne **1**:448, 1925.

The clinical pictures of thyroid disease range from the severe hyperfunction of exophthalmic goiter to the hypofunction of myxedema. In the relation between the thyroid gland and the infectious diseases and tuberculosis, it is the milder grades of hypofunction and hyperfunction that are important.

In fifty-three cases of tuberculosis no instance of hyperfunction was found, and only one of hypofunction. This was in a 53 year old man with ulcerative pulmonary tuberculosis, who improved during six months in the hospital.

Anatomic examination was made in forty-eight cases to determine a possible relation between the thyroid and pulmonary tuberculosis. Sclerosis was found in twenty-eight cases, colloid goiter in eleven, and no change in one. In thirty of these, there should have been insufficiency from the microscopic picture.

In the clinical picture, there are no symptoms corresponding to the pathologic findings. This absence of symptoms is remarkable. It may be explained by the hypothesis that one is dealing with a system of glands, instead of with a single one, and that the aspect of the morbid state depends on which gland is involved first. The thyroid is first involved when hyperfunction or insufficiency of that gland is part of the picture.

B. R. LOVETT.

SYMPATHETIC SYSTEM CHANGES IN DISEASES OF ENDOCRINE SYSTEM. B. N. MOGILNITZKY, Virchows Arch. f. path. Anat. **257**:765, 1925.

Because of the close interrelationship of the vegetative nervous system and the system of endocrine organs, disease of the latter leads to secondary degenerative changes in the former.

O. T. SCHULTZ.

BLOOD AND SYMPTOMATIC CHANGES FOLLOWING THE INTRAVENOUS ADMINISTRATION OF A VARIETY OF AGENTS AND SOLUTIONS. P. J. HANZLIK, F. DE EDS and M. L. TAINTER, Arch. Int. Med. **36**:447, 1925.

Intravenous injections into dogs of small and large doses of the following substances caused definite and important changes in arterial blood, accompanied as a rule by disturbances in physiologic functions: 10 per cent sodium chloride solution, 85 per cent sucrose solution, 50 per cent dextrose solution, 18 per cent urea solution, 0.1 per cent agar solution, 6 per cent and 25 per cent acacia solution, 5 per cent gelatin solution, 3 per cent barium sulphate suspension, 0.5 per cent fullers' earth suspension, 5 per cent copper sulphate solution, 9 per cent calcium chloride solution, 21.7 per cent sodium iodide solution, 50 per cent sodium salicylate solution, 0.33 per cent arsphenamine solution and 5 per cent peptone solution.

The principal blood changes were:

A considerable though variable dilution immediately after injection, except after barium sulphate, peptone and histamine, which tended to cause concentration or to prevent dilution.

A tendency to acidify as indicated by lowering of p_H value reduction from 7.3 or 7.2 to 6.9 or 6.8 being common and the lowest value observed being 6.6. Changes from the original were influenced by ether anesthesia, collapse, etc. With some agents the changes were temporary, with others permanent.

Accompanying the tendency to acidity, there usually was a reduction in the carbon dioxide (total and alkali reserve) of the plasma, and the reduction appeared to be chiefly a function of the blood dilution. Since the concentration of total carbon dioxide was reduced, the reduction in p_H was not due to carbon dioxide and presumably not to blood dilution per se.

Of the fixed acids, lactic acid was generally increased when the p_H was lowered, and it appeared to be concerned with the tendency to acidity in part at least. Total phosphate was inconstant or variable, but the analyses were incomplete.

Ammonia was frequently increased with the increase in lactic acid. Sugar showed unimportant changes, and urea remained constant or showed unimportant fluctuations even after injections of 18 per cent urea solution.

Darkening of the blood, together with an increased sedimentation rate, agglutination and hemolysis occurred after agar, acacia, urea, gelatin, barium sulphate, fullers' earth, arsphenamine, copper sulphate, sodium iodide and sodium salicylate, except that there was no hemolysis with iodide and salicylate and no agglutination with urea. Darkening and agglutination occurred with dextrose; darkening with phosphate and agglutination with histamine; hemolysis with 10 per cent and 0.1 per cent sodium chloride solution, horse serum and histamine, and increased sedimentation with 10 per cent sodium chloride solution. Reduction or inhibition of increase in sedimentation rate was observed with calcium chloride, sodium bicarbonate and sodium phosphate. These phenomena indicate surface changes in, and injury to, the corpuscles.

Disturbances in physiologic functions were indicated from changes in blood pressure, pulse and respiratory rates, ranging from moderate to profound and frequently resulting in collapse and sometimes in death. Tremors, twitching of muscles and sometimes convulsions were observed, together with occasional increases in the temperature of unmorphinized dogs, salivation and diuresis.

Deaths occurred from injections of 40 per cent hexamethylenamine solution, hexamethylenamine and sucrose, acacia, agar, copper sulphate, arsphenamine, fullers' earth, calcium chloride preceded by acacia and sodium chloride, peptone, sodium iodide and sodium salicylate.

The blood and symptomatic changes were not due to the removal of small quantities of blood for analyses and were, therefore, due to the injections themselves. Induced asphyxia which was used as control of the method of estimating p_H invariably lowered the p_H values (tendency toward acidity).

Lowering of p_H values of the blood did not occur or occurred only irregularly after the injection of 0.9 per cent sodium chloride solution (p_H and carbon dioxide lowered in two out of five experiments) used as the vehicle or solvent for the various agents that were injected—0.1 per cent sodium chloride solution and Tyrode's solution. Increases in p_H (alkaline tendency) occurred after 1.5 and 5 per cent disodium phosphate solution, 9 per cent bicarbonate solution and 2 per cent citrate solution, though some dilution and some or no reduction of carbon dioxide (except after bicarbonate, which increased it) of the blood occurred. Lactic acid tended to be augmented in alkaline blood after the phosphate, bicarbonate and citrate, while ammonia tended to decrease.

It is suggested that the basis of the changes which resulted from physically and chemically unrelated agents rests on disturbances in important physical and chemical mechanisms of the blood and tissues.

S. A. LEVINSON.

POST-ANAESTHETIC HYPOGLYCAEMIA. A STUDY OF THE ETIOLOGY OF RECURRENT VOMITING. HUGH JOSEPHS, Bull. Johns Hopkins Hosp. **37**:376, 1925.

The curve of blood sugar, the excretion of acetone bodies and the respiratory quotients have been studied in a series of children who had undergone short periods of anesthesia. Hypoglycemia of moderate degree was found to occur with great regularity from eighteen to twenty-four hours after the anesthesia. This hypoglycemia was preceded usually, but not invariably, by an increase in the respiratory quotient, and was accompanied by an increased excretion of acetone bodies in the urine. These changes were greater than could be accounted for by starvation. The bearing of these results on the etiology of recurrent vomiting and the allied condition of "post-anaesthetic acidosis" is discussed.

AUTHOR'S SUMMARY.

STUDIES IN CALCIFICATION. II. DELAYED EQUILIBRIUM BETWEEN THE CALCIUM PHOSPHATES AND ITS BIOLOGICAL SIGNIFICANCE. L. E. HOLT JR., V. K. LA MER and H. B. CHOWN, J. Biol. Chem. **64**:567, 1925.

III. A QUANTITATIVE STUDY OF THE EQUILIBRIA CONCERNED WITH THE CALCIFICATION OF BONE, L. E. HOLT JR., Ibid., p. 579.

Blood serum is normally more than 200 per cent supersaturated with tertiary calcium phosphate.

The rate of deposition of bone is related to the ion product $[Ca^{++}]^3 \times [PO_4^{---}]^2$. This has less than the normal value in the blood serum of persons with active rickets, but is still sufficiently large to cause precipitation of tertiary calcium phosphate.

ARTHUR LOCKE.

A Biochemical Study of Bone Growth. II. Changes in the Calcium, Magnesium, and Phosphorus of Bone During Growth. F. S. Hammett, J. Biol. Chem. **64**:685, 1925.

III. Changes in the Composition of the Ash During Growth. Ibid., p. 693.

The calcium percentage in the bones of the female albino rat is greater than that in the bones of the male. The participation of magnesium in the development of bone differs from that of calcium or phosphorus.

The changes in the composition of the bone ash consist in increases in the calcium and decreases in the magnesium and phosphorus percentages. They occur, in albino rats, during the growth time of from 23 to 150 days of age, and are practically complete at the end of the puberal period.

Arthur Locke.

The Effect of p_H on the Oxygen Consumption of Tissues. A. E. Koehler and R. J. Reitzel, J. Biol. Chem. **64**:739, 1925.

The optimum p_H for oxygen consumption by minced tissue suspensions is from 7.4 to 7.5. Oxygen consumption is almost completely depressed at p_H values less than 4.5 or greater than 10. At the same p_H, various tissues have different rates of oxidative activity. Heart muscle is most active, liver tissue much less, and skeletal muscle still less.

Arthur Locke.

Sulphemoglobinemia. L. P. Garrod, Quart. J. Med. **19**:86, 1925.

In two cases of sulphemoglobinemia the nitroso-bacillus was obtained in culture from the stools. Examination by the same technic of stools in other diseases failed to reveal the bacillus. The onset of this condition appears generally to be insidious but may occasionally be abrupt. The principal symptom in most patients was either shortness of breath (thirteen cases) or pain of an anginal nature (eight cases). Cardiac enlargement was well marked in fourteen cases. The superficial arteries were obviously diseased in five cases. There was definite hypertension in eleven cases and an associated valvular lesion in eleven cases. Auricular fibrillation was present in five cases, and complete auriculoventricular block in one case. The condition appears generally to be due to a secondary fibrosis of the heart muscle. If the lesion is localized, the prognosis is favorable, but if it is part of a widespread degenerative process the outlook is grave. Recovery in two instances took place during the administration in large doses of a vaccine prepared from the nitroso bacillus. After recovery no growth of the organism could be obtained from the stools, and substances immune to it were found in the blood serum of both patients.

Pancreatic Fistula. M. Villaret and L. Justin-Besancon, Arch. d. mal. de l'app. digestif **15**:751, 1925.

Villaret and Justin-Besancon studied a fistula of the pancreatic duct, consecutive to a gastro-enterostomy, subtotal gastrectomy and exclusion of the pylorus, in a man, aged 43. The rhythm of the secretion of pancreatic juice appeared markedly changed; the assimilation of nitrogen, phosphorus and sulphur considerably reduced. The internal secretory function of the pancreas appeared unaffected. The pancreatic juice did not contain invertin; trypsin production seemed normal or enhanced. Insulin did not modify the secretion;

the influence of atropin was indirect. Injection of magnesium sulphate into the jejunum provoked the appearance of bile, without stimulation of the pancreatic secretion. The influence of hydrochloric acid was the reverse of this. No tendency to a psychic pancreatic secretion could be detected.

AUTHORS' SUMMARY.

Pathologic Anatomy

SPLENOMEGALY (TYPE GAUCHER) AND LIPOID-HISTIOCYTOSIS (TYPE NIEMANN). WILLIAM BLOOM, Am. J. Path. **1**:595, 1925.

Two cases are reported, that of a boy aged 6 years and that of a woman aged 42 years, in whom there was a history of long-standing increase in the size of the spleen, leukopenia, mild secondary anemia, and epistaxis in one case and uterine bleeding in the other.

Microscopically there were large pale cells which contained iron and gave no typical reactions with the usual lipoid stains in the spleen, liver and lymph nodes. These large cells had a marked longitudinal striation with Mallory's aniline blue connective tissue method. These two cases seem to be typical of Gaucher's disease.

Three cases of the condition first described by Niemann are reported in infants aged 18, 14 and 7 months. The history in the first two was of long continued disturbance in feeding and a failure of the infants to develop. The third patient died of meningitis at a comparatively early period in the disease. One case was recognized in vivo, and the patient improved a good deal for two months after splenectomy, but then began to fail again.

Anatomically these cases have a widespread infiltration of lipoid material in the reticulum cells of the spleen, lymph nodes and thymus, Kupffer cells, clasmatocytes of connective tissue, and the large cells in the alveoli and perivascular tissues of the lung. The large foam cells are also present in the arteries of the lungs, pancreas and kidneys, and in the branches of the portal vein. In sharp contrast to the Gaucher cells, these cells stain positively for the complex lipoids; they do not contain iron, and are markedly vacuolated after treatment with absolute alcohol. The absence of the large cells from blood smears can probably be explained on the basis of their being filtered out by the capillaries, especially those of the lungs.

Chemical analysis of these spleens is now under way, and will be reported on elsewhere.

AUTHOR'S SUMMARY.

SPONTANEOUS CENTRAL NERVOUS SYSTEM LESIONS IN THE LABORATORY RABBIT. LAURETTA BENDER, Am. J. Path. **1**:653, 1925.

Lesions are described that are so extensive and occur so frequently as to render the rabbit poorly suitable for many experiments on the central nervous system.

EXPERIMENTAL PRODUCTION OF GLIOSIS. I. EFFECTS ON THE NERVOUS SYSTEM OF THE RABBIT OF INTRAVENOUS AND INTRASPINAL INJECTIONS OF CHOLESTEROL EMULSION. LAURETTA BENDER, Am. J. Path. **1**:657, 1925.

The conclusions from this series of experiments as far as the nerve tissues are concerned are that a hypercholesterolemia in the relatively small amounts used here has no effect on the cells of the nervous system except possibly to increase the lipoid content of the phagocytic cells of the meninges or peri-

vascular spaces, or in focal lesions already present due to other causes. Introducing the cholesterol directly into the subdural space of the spinal cord causes a thickening of the dura and a marked increase in cells of the arachnoid space which are phagocytic and ingest the cholesterol, and a moderate increase in the glia cells of the periphery of the cord. Five weeks after the last injection the meningeal and arachnoidal reaction is not seen, although the gliosis persists.

AUTHOR'S SUMMARY.

EXPERIMENTAL PRODUCTION OF GLIOSIS. II. REACTION OF BRAIN TISSUE TO THE LIPOID FRACTIONS AND TO THE RESIDUE OF BRAIN EXTRACTS. LAURETTA BENDER, Am. J. Path. **1**:667, 1925.

These experiments have to some degree separated the various constituents which usually form a single picture in a lesion in the brain. To separate these constituents more completely, it will be necessary to obtain either more nearly pure extracts or to fractionate these more completely. Studies in the various stages in the development of lesions resulting from the present series of extracts might also be of value. The water-soluble extracts were not used in these experiments, and these may be important factors in the tissue reactions to lesions in the central nervous system. They include alkaloids, organic and inorganic acids, carbohydrates, amino-acids and other unknown substances.

AUTHOR'S SUMMARY.

EPITHELIAL HYPERPLASIA OF THE BREAST. G. L. CHEATLE, Ann. Surg. **82**:673, 1925.

The author draws a parallel between the epithelial changes in the skin caused by tar and the epithelial changes in the terminal ducts and acini of the breast. Four stages are described: (1) a desquamative epithelial hyperplasia; (2) papillomatous formation due to a nondesquamative epithelial hyperplasia; (3) a more pronounced epithelial hyperplasia in which the cells are morphologically malignant but are within bounds; (4) carcinoma. He considers this epithelial hyperplasia the result of chronic irritation, and he has demonstrated patency of the ducts from beginning to end, so that there is nothing to prevent the entrance of an irritant. The term chronic mastitis indicating inflammation should be replaced by "hyperplasia."

N. ENZER.

INTRATHORACIC TUMORS IN CHILDREN. H. L. DWYER and F. C. HELWIG, Am. J. Dis. Child. **30**:799, 1925.

An intrathoracic chondrosarcoma arising from the inner aspect of the fifth right rib is described in a boy, aged 12 years.

BASOPHILIC AGGREGATION IN THE NEW-BORN. A. FRIEDLÄNDER and CHARLOTTE WIEDMER, Am. J. Dis. Child. **30**:804, 1925.

The number of basophilic cells in the blood of the new-born was found to be between 15,000 and 18,000 per cubic millimeter, the normal for adult blood being reached by the tenth day.

BLOOD PLATELET COUNT IN INFANTS AND YOUNG CHILDREN. STAFFORD MCLEAN and JOHN P. CAFFEY, Am. J. Dis. Child. **30**:810, 1925.

The counts fluctuate between 200,000 and 550,000. In lymphatic leukemia the count was reduced.

BRAINS WITH TOTAL AND PARTIAL LACK OF CORPUS CALLOSUM; NATURE OF LONGITUDINAL COLLOSAL BUNDLE. C. DE LANGE, J. Nerv. & Ment. Dis. **62**:449, 1925.

A case of absence of corpus callosum is described in a boy who died at the fifth month without having gained weight though breast-fed. There was an extensive polygyria, the corpus callosum was absent, and the olfactory nerves and bulb could not be found. The formix was present on both sides. The microscopic appearance of the brain is described, and the literature on absence of the corpus callosum is reviewed.

HEREDITARY ABNORMALITIES OF VISCERA; KIDNEYS IN DESCENDANTS OF ROENTGEN-RAYED MICE. H. J. BAGG, Am. J. Anat. **36**:275, 1925.

The visceral abnormalities in the descendants of a group of mice treated with comparatively light doses of unfiltered roentgen rays on five consecutive days are mainly defects of the kidney, which may vary from a partial to a nearly complete atrophy of one kidney, to the congenital solitary kidney condition, and to complete absence of both kidneys. The right or left kidney may be affected with equal frequency, and there is apparently no sex difference in this respect. Animals with the congenital absence of both kidneys are born alive and are apparently of average weight and development in other respects. They live for about twenty-four hours. Blindness and various defects of the limbs, syndactylism, polydactylism, and especially club feet, are closely associated with abnormalities of the kidneys. One instance of situs inversus viscerum has been noted. Embryologic studies of young from strains with a high incidence of visceral abnormalities have shown that these defects are associated with blood extravasations, especially in the liver and testes, which are similar to those extravasations closely associated with the production of blindness and club feet. Selection has greatly increased the number of animals with visceral abnormalities in the experimental lines. The visceral defects are definitely inherited, are recessive to the normal, and when considered as one of the manifestations of a general tendency to abnormal structure, they approach the mendelian expectation in behavior.

EXPERIMENTAL STUDY OF AMYLOID FORMATION. H. SMETANA, Bull. Johns Hopkins Hosp. **37**:383, 1925.

Kuczynski's method of subcutaneous injection of nutrose produces amyloid with certainty.

The earliest stages in the formation of amyloid are readily demonstrated only by vital staining with intravenous injections of Congo-red.

Severe damage to the cells of the parenchyma, infiltration of cells in the periportal regions and in the capillaries of the liver, increase in the cells of the malpighian bodies of the spleen and cell infiltration about them are constantly seen before and during the appearance of amyloid.

Similarly there is destruction of connective tissue and elastic fibrils in the areas where amyloid appears.

Before the appearance of amyloid in parenchymatous organs there is a swelling of the cells of the vessel walls and of the connective tissue and fibrils of the reticulum with dissolution of the nuclei and fusion into a formless mass in which the first traces of amyloid appear.

The process is particularly well seen when the formation of amyloid is most rapidly forced.

The assumption of bacterial cooperation in the production of amyloid is unnecessary.

AUTHOR'S SUMMARY.

WHEN DO LUNGS RETURN TO NORMAL FOLLOWING EXPOSURE TO WAR GASES? A. R. KOONTZ, Arch. Int. Med. **36**:204, 1925.

The results of studies on dogs which were gassed with phosgene, mustard, lewisite, chlorin, chlopicrin and methyldichlorarsin show that in the great majority of animals gassed at lethal concentrations, no pathologic lesions can be demonstrated for from two months to a year after recovery. In a minority of instances, permanent lung damage is done; it is not widespread, but generally confined to small areas and in the form of patches of organization, thickening of the bronchial walls with loss of elasticity, or occasional closing of the bronchioles by organized exudate. All such damage ultimately results in fibrous tissue formation, and the amount of scar tissue can hardly affect the functional efficiency of the lungs.

S. A. LEVINSON.

GENERALIZED TUBERCULOUS ADENITIS WITH REPORT OF A CASE. LEO H. CRIEP and FRED C. NARR, Am. J. Med. Sc. **170**:822, 1925.

A case of a generalized tuberculous adenitis without any visceral tuberculosis is reported. The condition was of two years' standing, and the patient was becoming progressively better.

Clinically the condition may easily be confused with Hodgkin's disease, but biopsy and bacteriologic study will settle the diagnosis.

A review of the literature discloses but few such cases.

There is no explanation as to how the glands may become involved in such a process without any visceral involvement.

AUTHORS' SUMMARY.

SPONTANEOUS RUPTURE OF THE HEART. E. B. KRUMBHAAR and C. CROWELL, Am. J. Med. Sc. **170**:828, 1925.

From an analysis of twenty-two cases hitherto unpublished, and 278 cases reported by others, and from a survey of 354 further cases from the literature, totaling 654, the following conclusions may be drawn:

Spontaneous rupture of the heart is chiefly an accident to the left ventricle of the aged; in the aged it is practically always due to coronary disease. It most frequently occurs in an acute infarct of the anterior surface of the left ventricle following sudden thrombosis of an artery or one of its branches; or less frequently the infarct may follow gradual fibrotic occlusion of the lumen.

With severe coronary sclerosis and consequent myocardial degeneration (usually with more or less cardiac aneurysm), rupture may occur in an area not obviously necrotic and supplied by a patent artery. The bursting of a cardiac aneurysm has been observed but is rare. Evidence is presented to show that the formerly popular diagnosis of fatty degeneration is usually incorrect or open to serious question.

Other rarer causes of spontaneous rupture considered in this analysis are "ulceration," fatty infiltration, fibrosis, syphilis, abscess, brown atrophy, parasitic cyst, tuberculosis, melanotic sarcoma. Most of these are based on reports of little value on account of the antiquity or incompleteness of the data.

Evidence about the site and character of the tear is considerable and accurate, but the actual mechanism which produces rupture and the actual cause of death are not clearly understood.

All classes and occupations are liable, and the exciting causes are most diverse. Premonitory symptoms are frequent but not characteristic. Terminal symptoms are usually so abrupt that little treatment can be even attempted, and the antemortem diagnosis is seldom made.

AUTHORS' SUMMARY.

TISSUE CHANGES FOLLOWING DEPRIVATION OF FAT-SOLUBLE A VITAMIN. S. BURT WOLBACH and PERCY R. HOWE, J. Exper. M. **42**:753, 1925.

The specific tissue changes which follow the deprivation of fat-soluble vitamin A in albino white rats and in the human concerns epithelial tissues. This effect is the substitution of stratified keratinizing epithelium for normal epithelium in various parts of the respiratory tract, alimentary tract, eyes, and para-ocular glands and the genito-urinary tract. Other effects are atrophy of glandular organs, emaciation, localized edema of testes, submaxillary gland, and connective tissue structures of the lungs and focal myocarditis.

THE ALVEOLAR PORES OF PNEUMONIA. WILLIAM SNOW MILLER, J. Exper. M. **42**:779, 1925.

This study confirms the author's previously expressed opinion — pores are not normal, preformed openings.

SKIN REACTIONS TO ALTERNATE HEAT AND X-RAY EXPOSURES. JAMES A. HAWKINS and HARRY CLARK, J. Exper. M. **42**:785, 1925.

Different areas on the abdomen of the same guinea-pigs have been exposed to suberythema doses of soft roentgen rays, to heat of an intensity below the critical dose for the production of burns, and to both radiations in sequence.

The only effect of exposure to roentgen ray or heat alone was a slight scaling of the skin. The areas exposed to heat and irradiation developed well marked and persistent burns. The results were the same no matter in which sequence the agents were applied.

AUTHORS' SUMMARY.

RÔLE OF THE NONGRANULAR BLOOD LEUKOCYTES IN THE FORMATION OF THE TUBERCLE. ALEXANDER A. MAXIMOW, J. Infect. Dis. **37**:418, 1925.

The study of in vitro cultures of various tissues and of blood leukocytes inoculated with tubercle bacilli shows that the epithelioid and giant cells of the tuberculous lesions have the same double origin as the polyblasts or mononuclear exudate cells in common or purulent inflammation. They arise partly from local fixed elements — the histiocytes of the respective tissue (resting wandering cells or clasmatocytes, reticular cells, cells of Kupffer, "endothelial" cells of the sinuses in the spleen, etc.), partly from the migrated (or local, if available), nongranulated, i. e., lymphoid white blood corpuscles — both monocytes and lymphocytes. According to the tissue and to the special circumstances of the case, the relative number of the epithelioid cells of histiocytic and of lymphoid descent may vary. If there are no leukocytes available, the epithelioid cells will be of purely local, histiocytic origin. This is, for instance, the case in the cultures of the lung tissue inoculated with tubercle bacilli described by Dr. Lang in a paper published in the present volume of *The Journal of*

Infectious Diseases. If, on the contrary, as in our cultures of leukocytes, or, for instance, in the early stages of tuberculosis, following the intravenous injection of bacilli, as described by Yersin and Borrel, only leukocytes are available near the bacilli, the primary tubercles will consist only of transformed lymphoid cells, lymphocytes and monocytes. No sharp discrimination between monocytes and lymphocytes could be made regarding their rôle in the formation of the tubercle. The monocytes respond more promptly to the stimulus and, being larger and better prepared for the defense reaction, sooner reach the fully developed epithelioid stage. The lymphocytes are slower, but nevertheless they follow in the same way, and sooner or later join the monocytes in their transformation into epithelioid cells.

AUTHOR'S SUMMARY.

EFFECTS OF DIPHTHERIA TOXIN ON THE MYOCARDIUM OF GUINEA-PIGS. CARL W. APFELBACH, J. Infect. Dis. **37**:443, 1925.

The changes in the myocardium of guinea-pigs after injection of diphtheria toxin subcutaneously resemble the changes described in the myocardium in human diphtheria, but they are in general not as extensive.

By direct injection of the myocardium, extensive degenerative and inflammatory changes can be produced in the guinea-pig equal in intensity to those found in human diphtheria. The outstanding changes are retrogressive (cloudy swelling, fatty change and necrosis). Infiltration of leukocytes with degenerative changes occur, but in the myocardium of guinea-pigs degeneration, proliferation and exudation were not commonly observed together in the same regions.

The degenerative changes in the skeletal muscles, liver and kidneys, as represented by the amount of fat that can be stained with sudan 3, are less than those in the myocardium.

AUTHOR'S SUMMARY.

THE NORMAL WEIGHT OF THE HUMAN THYMUS. ALLEN B. BRATTON, J. Path. & Bact. **38**:609, 1925.

Bratton studied 337 selected records from the London Hospital Pathological Institute, all of healthy young persons under 16 years of age, who died within twenty-four hours from accidents, burns, scalds, asphyxia under anesthetics, or the immediate results of these. The cases were divided into age groups and subdivided into groups of males and females.

He found that the absolute weight of the thymus increases rapidly during the first two years of life, then changes little until the seventh year, when it again increases, to fall slightly after the eleventh year.

For the first six months the weight of the thymus increases relatively to the body and then rapidly decreases; after the fifth year the relative decrease progresses at a slower rate, and is interrupted by a temporary increase during the eighth year.

In the male the thymus is slightly heavier at birth and during the first four years of life. After this the weight is approximately equal in the two sexes until the eleventh year. After the eleventh year the thymus tends to be heavier in the female.

ERNEST M. HALL.

ON LIVER NECROSIS AND CIRRHOSIS PRODUCED EXPERIMENTALLY BY COAL TAR. JAMES DAVIDSON, J. Path. & Bact. **28**:621, 1925.

Coal tar (pix liquida) was applied to the ears of rabbits or injected in ethereal solutions subcutaneously, and obtained necrosis of the liver cells. The

acute changes were similar to those in acute yellow atrophy in man, while the chronic changes resembled those of atrophic cirrhosis. Davidson suggests that the changes observed in acute yellow atrophy, subacute yellow atrophy and atrophic cirrhosis of the liver may be different stages in the same process.

The regenerated tissue was also susceptible to the irritant. In some cases the arrangement of the regenerated liver cells were irregular and closely resembled adenomatous tumor growth. Here is an experimental demonstration of the possible connection between cirrhosis and tumor of the liver.

ERNEST M. HALL.

CHANGES IN ARTICULAR SURFACES IN TUBERCULOUS ARTHRITIS. D. B. PHEMISTER, J. Bone & Joint Surg. **7**:763, 1925.

In the earlier stages of tuberculous arthritis the articular cartilage usually is destroyed most extensively along its free articular surfaces by granulations from the synovial membrane. In the regions of contact and pressure surface destruction does not take place, and the cartilage is preserved longest. As the disease progresses, subchondral granulations develop which absorb the articular cortex and attack the cartilage from beneath. In severe tuberculous arthritis there may be early necrosis and caseation of the overgrowing synovial granulations, so that there is little or no destruction of articular cartilage along its free surfaces. In this event the destruction of articular cartilage is brought about mainly by the subchondral granulations, which do not undergo early necrosis and caseation and do not present the usual histologic picture of tuberculous tissue. The bony involvement along the articular surface may be primary or secondary. When primary, the dead bone may break down, leaving a cavity, or may persist and form a sequestrum which has articular cortex and, in some instances, cartilage preserved on it, and is denser than the surrounding living bone which subsequently atrophies. Secondary involvement of bone along the articular surfaces may lead to destruction of the entire articular cortex by superficial caries or to more or less extensive and deep areas of necrosis at the points of greatest pressure in the joint. This deep invasion is often bilateral and is followed by the formation of "kissing sequestrums," which may be mistaken for primary foci of osseous infection.

ABNORMAL ARTERIOVENOUS COMMUNICATIONS, ACQUIRED AND CONGENITAL. THE EFFECTS OF ABNORMAL ARTERIOVENOUS COMMUNICATIONS ON THE HEART, BLOOD VESSELS AND OTHER STRUCTURES. M. R. REID, Arch. Surg. **11**:25, 1925.

Collateral circulation is greater from an arteriovenous fistula than from simple occlusion of a vessel. Proximal to the fistula the artery usually dilates, the walls become thin, and atrophy of muscular and elastic tissue takes place. True aneurysms occur proximal to the fistula. The proximal dilatation may extend back to the heart causing hypertrophy and dilatation. Such vascular lesions often cause increased length of limb especially before the epiphyses are ossified. Beyond the fistula the circulation is impaired. Kidneys of dogs did not survive complete reversal of circulation.

N. ENZER.

INTESTINAL DIVERTICULA. E. S. SPRIGGS and O. A. MARXER, Quart. J. Med. **19**:1, 1925.

In 1,000 consecutive radiologic examinations of the alimentary canal, duodenal diverticula have been detected by Spriggs and Marxer thirty-eight times. In thirty-two cases the diverticulum was single; in six, two or more

diverticula were present. One patient had six duodenal diverticula as well as several in the jejunum. In all, fifty-one duodenal pouches were recognized in the thirty-eight patients concerned, one arising from the first part of the duodenum, thirty from the second, sixteen from the third, and four from the fourth part. Diverticula of the jejunum were observed in seven patients. In four of these there were also pouches in the duodenum. In the ileum seven diverticula were found (excluding Meckel's diverticulum). Diverticulosis of the appendix occurred six times. Diverticulosis of the large intestine was recognized in 100 patients. A prediverticular state can be recognized radiologically, characterized by fixity of the affected part of the bowel wall, with small irregularities. This is the first stage of the disease, at which the minute hernias begin to develop. The second stage of diverticulosis is one of formed diverticula. The third stage is termed diverticulitis. Inflammation has now spread from the pouches to the walls of the bowel and surrounding parts.

INTESTINAL DIVERTICULA. E. T. SPRIGG and O. A. MARXER, Quart. J. Med. **19**:73, 1925.

In roentgen-ray examination of the alimentary tract of 1,000 consecutive patients, intestinal diverticula were found in 143. In thirty-eight, duodenal diverticula were present, six of which were multiple, and the majority were in the second portion. In discussing the etiology, the authors point out that nearly all duodenal diverticula have been found in elderly patients, and in some they were able to observe an increase in the size of the diverticulum after middle age. This they think is in favor of their being acquired in nature rather than congenital. Oral sepsis and focal infection were frequently associated. Diverticula of the jejunum exclusive of Meckel's, was noted in seven persons, and very small projections resembling the early stage of multiple colic diverticulosis were found in the ileum in seven. Diverticulosis of the large intestine was found in 100 of the 1,000 patients; 71 per cent were in men and the average age was 58 years. The average age of the patients in the series was 45 years. The most frequent situation was the pelvic colon. The authors distinguish a prediverticular stage characterized by fixity and irregularity of the bowel wall as shown by the roentgen ray, a second stage of developed diverticula and a third stage of diverticulitis. They consider focal infection and stasis important points in the etiology. Seventy per cent of the patients had spondylitis, and a large percentage had oral sepsis. The article is extremely well written. Chapters on the literature, symptoms, diagnosis, roentgen-ray technic, treatment and results are given, and a bibliography. The plan of the article is highly commendable.

N. ENZER.

APPEARANCES OF MAMMALIAN ERYTHROCYTES UNDER DARK GROUND ILLUMINATION. W. G. MILLAR, Quart. J. Exper. Physiol. **15**:253, 1925.

No signs of internal structure could be seen by Millar in the human erythrocyte, even under the best conditions of dark ground illumination, an objective of numerical aperture 1-32 being used.

OBSTRUCTION OF RENAL TUBULES DURING EXCRETION OF HEMOGLOBIN. L. L. BAKER and G. C. DODDS, Brit. Exper. Path. **6**:247, 1925.

Two cases of intrarenal obstruction caused through blood transfusion are described and compared with the intrarenal obstruction of blackwater fever. A series of in vitro experiments proved that hemoglobin is thrown out of

solution when (*a*) the reaction of the medium is not more than about p_H 6, and (*b*) the sodium chloride content is about 1 per cent or over. From these experiments it would appear that hemoglobin is excreted in solution in the globerular transudate. After concentration in the tubules the acidity and the salt concentration increase, with the result that the pigment is precipitated, probably in the form of hematin. This theory would explain the production of intrarenal obstruction in cases of the type described and in blackwater fever. A suggestion for the treatment of these conditions, based on the above conclusions, is offered; namely, the production of alkaline diuresis.

INFORMATION BY SECTIONS IN SERIES DURING THE IRRADIATION TREATMENT OF CANCER OF THE UTERUS. G. ROUSSY, R. LEROUX and Y. L. WICKHAM, Rev. méd. de la Suisse Rom. **45**:458, 1925.

Examinations of tissue from cervical carcinomas in two somewhat similar cases disclosed, in the one resulting in early death, a peculiar fragility of the vascular connective tissue stroma, while in the other, which remained cured for at least three years, there was marked sclerosis of the blood vessels. The usual features of cell degeneration and stimulated proliferation are present, but vary so greatly that observations are of value only by comparison with untreated tissue. Histologic changes become most evident in about fifteen to twenty days after roentgen-ray treatment, or in six to eight days after radium applications. Only in conjunction with clinical and other findings can these observations be given their proportionate value.

G. B. RHODES.

PNEUMATOSIS OF THE INTESTINAL PERITONEUM. ATTEMPTED EXPLANATION OF THE CAUSE. P. MASSON, Rev. méd. de la Suisse Rom. **45**:470, 1925.

After brief investigation of the literature with special reference to the theories of the cause of gas cysts, particularly in man, a new theory is offered. Absorption of acids, possibly lactic, by the mucosa over a long period of time may allow of a collection there and in the lymph vessels with subsequent freeing of carbon dioxide. This accumulated carbon dioxide diffuse to a state of equilibrium with the gases of the blood and lymph spaces. No supporting experiments have been made.

G. B. RHODES.

ENDOMETRIOMA AND UTERINE DYSEMBRYOPLASIA. LETULLE, TUFFIER and LAMBERT, Bull. Acad. de méd., Paris **94**:1035, 1925.

Letulle, Tuffier and Lambert report, among others, a case of interstitial endometrioma of the uterus, also an aberrant endometrioma beneath a laparotomy scar and another in the groin. The age of the women ranged between 35 and 52. In accord with Cullen, the authors believe that the interstitial endometrioma represents a hyperplastic malformation involving only a certain portion of the uterine mucosa. The old term for it, adenomyoma, is incorrect. The aberrant or extra-uterine endometrioma behaves like a supernumerary uterus. All these malformations are apparently due to some disturbance in the fusion of the Müllerian ducts at the third month of embryonal life.

THE NATURE AND ETIOLOGIC DETERMINATION OF THE ENDOCARDITIC PROCESS. BINDO DI VECCHI, Arch. di pat. e clin. med. **4**:241, 1925.

The classical conception of endocarditis, degenerative or inflammatory lesions in the valve tissues followed by thrombotic depositions, is confirmed by recent

studies. The formation of thrombi is an accessory factor and may be entirely absent under some conditions. The localization of the bacteria in the valves is determined, not only by a certain "electivity" on the part of the organisms, but also by mechanical and traumatic factors, as variations in blood pressure, anomalies of blood flow due to previous valvular insufficiencies from myocarditis. The mechanism of production of the thromboses is analyzed, and variations in the process attributed to variations in the morphology and chemistry of the blood and bone marrow. The influence of age and individual constitution in determining endocarditis, especially the influence of the endocrine glands, in increasing the liability to thromboses is discussed.

A. GIORDANO.

THE PERICARDIAL DIVERTICULUM. WOLDEMAR LAUER, Centralbl. f. allg. Pathol. u. path. Anat. **36**:353, 1925.

A diverticulum was found at necropsy, extending from the upper right hand part of the pericardium. It was 8 cm. long, contained clear fluid, and communicated with the main pericardial sac.

B. R. LOVETT.

THE PATHOGENESIS OF ULCUS PEPTICUM VENTRICULI AND DUODENI. Y. NAKASHIMA, Ztschr. f. Ges. Exper. Med. **47**:4, 1925.

The author's experiments lead him to the conclusion that erosions are formed in the mucosa of the stomach following the injection of large doses of pilocarpin into rabbits suffering from general toxemia, and when the blood pressure is normal. This corroborates the observations of Westphal.

When a 1 per cent (or weaker) solution of pilocarpin is painted on the wall of a rabbit's stomach, a marked circular contraction takes place at the point of application. If this procedure is continued for any length of time, typical hemorrhagic erosions result, and this is held to be proof that hemorrhagic erosions follow marked muscular contractions of the stomach.

When large doses of pilocarpin are injected into dogs, hemorrhages in the mucosa of the intestinal tract and hemorrhagic erosions appear in the mucosa of the stomach, and these take place later than in rabbits and monkeys because the musculature of the dog stomach is thicker.

Subcutaneous injection into a dog of a combination of pilocarpin, epinephrin and morphine results in marked reduction of the contractility of the intestine, and at the same time a corresponding increase in the contraction of the stomach, so much so that a relatively light degree of hemorrhagic erosions are seen in the stomach mucosa. Deep hemorrhagic erosions may result from this procedure, but no chronic ulcus is formed.

Daily injections of pilocarpin and epinephrin into a monkey in such doses that the animal does not die of poisoning, results in various forms of erosions in the stomach up to the chronic perforating ulcer.

S. A. LEVINSON.

EXPERIMENTAL AND PATHOLOGIC STUDIES ON PROGRESSIVE MUSCULAR ATROPHY. K. KURE, S. HATANO, T. SHINOSAKI and T. NAGANO, Ztschr. f. Ges. Exper. Med. **47**:77, 1925.

The authors' experimental and clinical studies indicate that progressive spinal muscular atrophy and amyotrophic lateral sclerosis are the result of degeneration of motor ganglion cells in the anterior horn of the spinal cord, while the sympathetic system is slightly involved or remains intact. Progressive muscular dystrophy is the result of disturbance of the autonomic system.

S. A. LEVINSON.

Pathologic Chemistry

ON THE DISTRIBUTION OF INJECTED SULFATES IN TISSUES. W. DENIS and S. LECHE, J. Biol. Chem. **65**:565, 1925.

Hypertonic solutions of sodium sulphate were administered to dogs by intravenous injection. There was little adsorption of the sulphate ion in the muscles or viscera, although even two hours after injection the sulphate content of the blood was still ten times the initial value.

ARTHUR LOCKE.

THE ISOLATION FROM BLOOD OF A HITHERTO UNKNOWN SUBSTANCE, AND ITS BEARING ON PRESENT METHODS FOR THE ESTIMATION OF URIC ACID. G. HUNTER and B. A. EAGLES, J. Biol. Chem. **65**:623, 1925.

A new substance of the empirical formula $C_5H_{11}N_2O_3$, believed to be a simple pyrimidine nucleoside, is present in human erythrocytes to the extent of 10 to 12 mg. per hundred cubic centimeters of whole blood. This substance is mainly responsible for high, direct "uric acid" values and is separable from uric acid in blood filtrates by the precipitation method of Folin and Wu.

ARTHUR LOCKE.

STUDIES OF GAS AND ELECTROLYTE EQUILIBRIA IN BLOOD. VIII. THE DISTRIBUTION OF HYDROGEN, CHLORIDE, AND BICARBONATE IONS IN OXYGENATED AND REDUCED BLOOD. D. D. VAN SLYKE, A. B. HASTINGS, C. D. MURRAY and J. SENDROY, JR., J. Biol. Chem. **65**:701, 1925.

The distribution of the diffusible ions, H^+, Cl^-, and HCO_3^- between serum and cells of horse blood has been studied over the p_H range 7.0 to 7.6, and in oxygenated and reduced blood.

ARTHUR LOCKE.

FURTHER STUDIES ON THE PARATHYROID HORMONE. J. B. COLLIP and E. P. CLARK, J. Biol. Chem. **66**:133, 1925.

A method of purification of the parathyroid hormone is described. A dry, amorphous powder was obtained which was slightly soluble in absolute alcohol. The material precipitated iso-electrically at p_H 4.8 and contained 15.5 per cent of nitrogen, some iron and sulphur.

ARTHUR LOCKE.

THE CONCENTRATION OF CHLORIDES IN THE GLOMERULAR URINE OF FROGS. J. T. WEARN and A. N. RICHARDS, J. Biol. Chem. **66**:247, 1925.

The concentration of chlorides in the glomerular urine of frogs is slightly greater than that in the plasma and much greater than that in the bladder urine.

ARTHUR LOCKE.

THE SUGAR CONTENT OF BLOOD. B. K. HARNED, J. Biol. Chem. **65**:555, 1925.

The Folin-Wu reactions for blood sugar are applied to blood filtrates from mercuric nitrate precipitation. The blood sugar values average from 17 to 25 per cent less than those found by the regular Folin-Wu procedure, but agree closely with those given by the new Benedict method.

ARTHUR LOCKE.

CHARACTERISTIC CHANGES IN BLOOD CHEMISTRY IN WHOOPING COUGH. JOSEPH C. REGAN and ALEXANDER V. TOLSTOOUHOV, J. A. M. A. **86**:181, 1926.

A total of 200 analyses of the blood have been made in whooping cough. Distinct and apparently significant changes have been encountered, the most characteristic of which were: (1) a lowering of the hydrogen ion concentration of the blood and (2) a diminution of the inorganic phosphorus content.

AUTHORS' SUMMARY.

CONCERNING THE STABILITY OF THE ACID-BASE EQUILIBRIUM OF THE BLOOD IN PREGNANT ANIMALS. WILLIAM DEB. MACNIDER, J. Exper. Med. **43**:53, 1925.

The acid-base equilibrium of the blood as indicated by determinations of the reserve alkali of the blood remains constant in nonpregnant animals at different age periods. This statement does not imply that the acid-base balance of such animals at different age periods is a stable balance.

In pregnant animals of the same age periods as the control animals there may develop an instability of this equilibrium which is either associated with the occurrence of a renal injury and which may be looked on as a retention phenomenon, or which arises independently of such an injury. In the latter group of animals the disturbance in the equilibrium increases in frequency and is earlier in its appearance in the gestation period as the age of the organism increases.

In old and in senile pregnant animals some physiologic mechanism other than that of the kidney becomes unable to stabilize the acid-base equilibrium of the blood, with the result that as the pregnancy advances this physiologic state of the organism (gestation) becomes pathologic.

AUTHOR'S SUMMARY.

NATURE OF URINARY PROTEIN. E. R. CARLING and H. CARLILI, Lancet **2**:917, 1925.

Evidence is submitted that the protein excreted in the urine in various conditions is not always identical. In the twelve cases of "albuminuria of pregnancy" without convulsions investigated, the specific rotation of the urinary albumin averaged 55.81 degrees, and thus agreed with that found for human serum albumin under similar treatment; namely, —54.47 degrees. A similar close agreement in specific rotation, namely, —54.25 degrees, was found in five cases of proteinuria not associated with pregnancy. On the other hand, the fourteen cases of eclampsia investigated were sharply divided into two groups, one group of six having an average ^{a}D of 56.37 degrees, and the other group of eight having an average ^{a}D of —38.5 degrees. The optical activity of the albumin in the former group agrees well with that of serum albumin (—54.47 degrees), while that in the latter approximates closely that of cow's lactalbumin (—41.17 degrees). Accordingly, it is suggested (*a*) that in certain types of eclampsia the urinary albumin may be mainly lactalbumin; (*b*) that eclampsia may be an anaphylactic reaction due to the circulation in the blood of this foreign protein; and (*c*) that the mammary gland may be an important factor in the causation of eclampsia.

SOURCE OF PROTEIN IN ALBUMINURIA OF EXPERIMENTAL NEPHRITIS. C. H. KELLAWAY, G. F. S. DAVIES and F. ELEANOR WILLIAMS, Australian J. Exper. Biol. M. Sc. **2**:139, 1925.

In acute uranium nephritis in cats, in which the damage is predominantly tubular, there was found in the urine by means of the anaphylactic reaction

soluble proteins other than those derived from the plasma and apart from casts and epithelial débris. This protein is believed to be of renal origin.

Crystals in Cerebrospinal Fluid. Beck, Bruxelles méd. **5**:1484, 1925.

Cholesterol crystals in large numbers were observed, apparently for the first time, in the cerebrospinal fluid. The patient was a girl, aged 4, who had meningitis.

The Lipoidal Nature of Eosinophil Granules. A. Neumann, Klin. Wchnschr. **4**:1552, 1925.

The eosinophil substance is soluble in weakly acid, anhydrous alcohol. Its further nature was not determined.

Arthur Locke.

Blood Sugar and Pulmonary Tuberculosis. P. Hecht, Klin. Wchnschr. **4**:1595, 1925.

Blood sugar determinations were made on persons with tuberculosis of the lung. The fasting values in the majority were hypoglycemic. No explanation is advanced.

Arthur Locke.

The Normal Bilirubin Content of Blood Serum. J. Förster, Klin. Wchnschr. **4**:1688, 1925.

The bilirubin content of human blood serum can vary from 0.2 to 1 mg. per cent without the association of hemolytic processes or pathologic changes of the liver and bile passages.

Arthur Locke.

The Hexosephosphoric Acid of the Blood in the Normal and Diabetic Organism and Its Relation to Epinephrin and Insulin. H. Lawaczeck, Klin. Wchnschr. **4**:1858, 1925.

About 10 per cent of the glucose of normal blood is combined with phosphoric acid, but the amount combined is not regulated by the total sugar content. The quantity of hexosephosphoric acid formed determines the quantity of carbohydrate combustion. Subcutaneous injection of epinephrin raises the blood sugar content, but markedly lowers the content of hexosephosphoric acid in the blood. Insulin has a diametrically opposite effect. The injection of insulin stimulates the secretion of epinephrin and vice versa. Some "insulin-refractory" patients react allergically to insulin, the injection serving only to distort the epinephrin insulin equilibrium with a compensatory stimulation of epinephrin production.

Arthur Locke.

Lactic Acid Elimination to Carcinosis. K. Glaessner, Klin. Wchnschr. **4**:1868, 1925.

The intravenous injection of glucose into carcinomatous mice produces an elimination of lactic acid in the urine. This is not the case with normal or sarcomatous mice, nor when sugar has not been previously injected. Lactic acid elimination may be produced in enchondromatous mice, but does not persist.

Arthur Locke.

MICROCHEMICAL DETECTION OF UREA IN TISSUES. A. OESTREICHER, Virchows Arch. f. path. Anat. **257**:614, 1925.

Oestreicher treated thin pieces of tissue with 6 per cent. xanthydrol in glacial acetic acid for the detection of urea, according to the technic of Stübe. The amount of crystalline, insoluble dixanthylurea present in the tissues was compared when the patients died of uremia, when they died without uremia but when necropsy revealed varying grades of renal damage, and in a series of persons who had died of various conditions. In normal persons the xanthydrol reaction shows the presence of a slightly greater amount of urea in the kidneys than in the other organs. In urea retention the urea is uniformly increased in all the tissues except in the white matter of the central system. A moderate increase was found in carcinoma and in diseases accompanied by high fever, the increase in such cases being due to toxic destruction of tissue protein. A similar moderate increase was found in renal disease which had not been associated clinically with uremia. A marked increase was found in all cases of uremia, such a great increase in tissue urea being considered so constant and such characteristic evidence of true uremia that it permits the pathologist to establish the diagnosis of uremia. An exceptionally high urea content was seen in the ganglion cells of the medulla. In general, the urea content of the tissues, as determined by the xanthydrol reaction, runs parallel with the urea content of the blood.

O. T. SCHULTZ.

ON THE ALTERATIONS OF BLOOD SUGAR WITH REPEATEDLY ADMINISTERED DOSES OF SUGAR BY MOUTH. N. HOSAKA, Sc. Rep. Govt. Inst. Infect. Dis., Tokio **3**:159, 1924.

Experimenting with normal rabbits and rabbits in which the pancreas had been extirpated, the author found that: (1) With repeated administrations of dextrose in normal animals there is a gradual diminution of blood sugar maximum. The highest maximum point corresponded with the highest dosage of the sugar. (2) A second administration of a large dose of dextrose to an animal which had previously utilized an earlier small dose, given after fasting, produces a maximum blood sugar far less than the normal result from the same dosage. (3) If a second administration of dextrose is made before the decline of blood sugar is completed, a maximum blood sugar is obtained greater than when the second dose follows the complete decline. (4) If a two hour period is allowed to elapse after the completion of the decline and a second dose of the same amount is then given, a lower maximum of blood sugar is reached, but the complete decline to normal takes a longer period. (5) In animals with extirpated pancreas the normal blood sugar content is higher than in controls. On administration of dextrose to these there is found a still greater content of blood sugar with a greatly increased period of persistence; also the appearance of glycosuria.

H. E. EGGERS.

A BIOCHEMICAL STUDY OF THE ACTION OF LYMPHOCYTES. S. OHYAMA, Sc. Rep. Govt. Inst. Infect. Dis., Tokio **3**:173, 1924.

Basing his conclusion on in vitro experiments, the author found that: Extracts of lymphadenoid tissue are without any intrinsic lipatic or amylolytic power. They possess, however, the ability to activate pancreatic amylase and lipase. This they presumably do by protecting these ferments from tryptic digestion, and the same effect is achieved by other proteid-containing extracts.

Since the lymphocytes are the only migratory cells passing through the intestinal wall in considerable numbers, they would appear to be the principal source of such amylolytic and lipatic activation. The author, however, believes it unsafe to conclude that their intestinal action is solely of this nature.

H. E. Eggers.

Microbiology and Parasitology

Pyocyneus Meningitis After Lumbar Puncture. I. I. Levy and A. E. Cohen, J. A. M. A. **85**:1968, 1925.

In a man, aged 32, pyocyaneus meningitis occurred after a lumbar puncture without any preceding pyogenic infection. Spinal drainage and injections of autogenous serum were used in the treatment, and the patient recovered. Three somewhat similar cases are cited from the literature.

E. B. Perry.

Pneumococcic and Streptococcic Peritonitis: Report of Twenty-Three Cases in Infancy and Childhood. Benjamin Lipshutz and Harry Lowenburg, J. A. M. A. **86**:99, 1925.

Pneumococcic and streptococcic peritonitis is a comparatively frequent abdominal lesion in infancy and early childhood.

More than 90 per cent of the cases were preceded by a definite pharyngeal infection or coryza, the latter antedating the onset of the abdominal symptom by from four to seven days.

The clinical picture is characteristic. Differentiation of the streptococcic from the pneumococcic type can be made only by means of smears or a culture of the exudate.

The peritonitis always begins as a pelvic peritonitis.

Early operation is recommended to prevent any error in diagnosis and to give an outlet for the peritoneal exudate.

Authors' Summary.

The Interconvertibility of "Rough" and "Smooth" Bacterial Types. Edwin O. Jordan, J. A. M. A. **86**:177, 1926.

Single cell strains of paratyphoid bacilli of the R and S type can more or less regularly be made to yield cells of the opposite type by appropriate treatment. A nonvirulent strain can at will be converted into a virulent, and the virulent strain so produced possesses certain correlated characters, such as agglutinability and colony type formation, which distinguish it from the parent cell.

Author's Summary.

Trichinosis Encephalitis. George B. Hassin and Isadore B. Diamond, Arch. Neurol. & Psychiat. **15**:34, 1926.

Trichinosis may produce a typical picture of acute nonsuppurative meningoencephalitis. It produces marked degenerative and inflammatory reactive phenomena. The former are due to the toxins, the latter to the presence of *Trichinae*. Trichinae are harbored within large accumulations of cell elements — nodules, syncytia and perivascular infiltrations. The invasion of the brain by *Trichinae* occurs through the lymph and blood vessels. The elimination of *Trichinae* occurs by way of the adventitial channels into the subarachnoid space and the cerebral ventricles.

Authors' Summary.

GIARDIASIS (LAMBLIASIS): FIVE CASES. M. B. MARCELLUS, U. S. Veterans' Bur. Med. Bull. **1**:1, 1925.

Marcellus reports five cases presenting the usual symptoms, those of an acute or chronic enterocolitis or cholecystitis: namely, diarrhea of various degrees or occasionally constipation and irregular bowel movements; pain and tenderness in the upper part of the abdomen at the costal margin, and in both sides, sometimes more pronounced on the right side than on the left; nausea on eating and occasionally vomiting; general loss of weight; weakness and neurasthenia. Duodenobiliary drainage in four of these cases revealed many motile flagellates in the bile, and examination of the stools showed numerous ova and cysts of *Giardia intestinalis.*

EXTRACTS OF NORMAL TISSUES IN EXPERIMENTAL TUBERCULOSIS. RICHARD S. AUSTIN, J. Infect. Dis. **37**:256, 1925.

The inoculations of simple extracts, not incubated, of certain fresh normal organs of the rabbit appears to influence the development of experimental tuberculosis in rabbits. The extracts of different kinds of organs vary considerably as to the amount of influence displayed. Extracts of the suprarenal and lung frequently would seem to retard the development of the disease; those of the heart and liver produce less effect as a rule, while extracts of spleen and kidney exert little or no influence. The freshness of the organs used, the short time utilized in preparing the extracts, the avoidance of incubation and the preservation of the extracts, between inoculations, at icebox temperature, make it seem possible that the more or less protective substances present in some of the organ extracts exist in the organs before removal from the animal.

AUTHOR'S SUMMARY.

INDUCED AND NATURAL TRANSMISSION OF BLACKHEAD IN THE ABSENCE OF HETERAKIS. ERNEST EDWARD TYZZER and JANE COLLIER, J. Infect. Dis. **37**:265, 1925.

No case of blackhead has developed in large numbers of incubator hatched turkeys kept in clean compartments and fed on sterilized food, so that there is no indication that the infection is transmitted through the egg. Turkeys reared under such conditions remain free from intestinal amebas and flagellates for long periods. The early appearance of coccidiosis under conditions of strict isolation indicates that the coccidium of the turkey is transmitted either through the turkey's egg or on the shell of the latter. Blackhead of the type which occcurs naturally may result from feeding material from active liver lesions but is produced more regularly by the rectal injection of such material.

The passage of the blackhead protozoon into the turkey's cecum in sufficient numbers appears to be the only condition necessary for the invasion of the tissues in young turkeys, so that lowered resistence and local injury are without etiologic significance.

It is apparent from the present experiments that the blackhead protozoon is discharged from acutely infected turkeys in a form which is capable of producing infection if ingested at once, but which persists for only a short time outside the body. The possibility of the direct transmission of the disease

from infected to healthy stock indicates the importance of the isolation of the former.

The results seem to show the complete independent biologic specificity for certain glucoproteins isolated from mammalian sources and that a certain amount of relationship seems to exist between two glucoproteins of the hen's egg.

EFFECT OF MEDIUM ON RATE OF MULTIPLICATION, VIRULENCE AND HEAT SUSCEPTIBILITY OF HEMOLYTIC STREPTOCOCCUS. T. D. BECKWITH and E. J. ROSE, J. Infect. Dis. **37**:277, 1925.

A certain strain of hemolytic streptococcus has been cultured continuously in rabbits by intrapleural injection. This is the passage strain. It has been carried on blood agar. The latter is the stock strain. Proliferation of the passage strain in infusion broth is much more active than that of the stock strain in the same medium.

The minimum lethal dose for normal rabbits of 3,500 to 4,000 Gm. weight by intrapleural injection of these two strains differs greatly. Three hundred organisms of the passage culture kill, while 166,000,000 organisms of the stock culture are not fatal.

The thermal death point of the passage culture is lower than that of the stock culture by approximately 5 C. when the numbers of organisms thus treated are approximately the same in both instances. A similar difference is noted also when inactivated serum with broth is substituted for the milk. This same difference in heat susceptibility persists when the reaction of the medium is altered through a range of p_H 5.8 to p_H 8.8.

This difference in relative susceptibility disappears when chemical germicides are used.

EFFECT OF INSULIN ON CULTURES OF B. BULGARICUS AND B. ACIDOPHILUS. ARTHUR ISAAC KENDALL and MITZUTERU ISHIKAWA, J. Infect. Dis. **37**:333 (Oct.) 1925.

At the present time, with available evidence, the definiteness of the effects of adding insulin to milk-glucose-insulin cultures of *B. bulgaricus* and *B. acidophilus*, as shown by detectable increase in titrable acidity, remains an open question.

AUTHORS' SUMMARY.

EFFECT OF INSULIN ON BACTERIAL METABOLISM. ARTHUR ISAAC KENDALL and MITZUTERU ISHIKAWA, J. Infect. Dis. **37**:337, 1925.

It would appear that insulin, under the conditions imposed by the experiment, had no appreciable effect on the utilization of glucose for energy by a considerable number of bacterial types.

AUTHORS' SUMMARY.

A PATHOGENIC SUBTILIS BACILLUS FROM A PATIENT WITH CHRONIC TUBERCULOSIS. H. C. SWEANY and MAX PINNER, J. Infect. Dis. **37**:340 (Oct.) 1925.

This appears to be the second time that a subtilis bacillus, pathogenic for animals, has been isolated from human sources other than the eye. This bacillus was isolated from most of the lesions and the principal body fluids; it grew at first only on medium containing blood, where it produced a large hemolytic zone,

and it killed white rats. These results suggest that subtilis bacilli in cultures from human sources perhaps should not be discarded offhand as always being due to mere contamination.

AUTHORS' SUMMARY.

TOXIN PRODUCTION BY CLOSTRIDIUM BOTULINUM IN CANNED FOODS. LUTHER THOMPSON, J. Infect. Dis. **37**:344, 1925.

Twenty-three kinds of food were inoculated with detoxified spores of 4 strains of *Clostridium botulinum*. Those found to be regularly toxic with all strains are: red kidney beans, lima beans, hominy, peas, sweet potato, salmon and shrimp. Those irregularly toxic are: asparagus, beets, pumpkin and spinach. The acid fruits and the very acid vegetable products, such as sauerkraut and dill pickles, did not become toxic.

Certain extracts and liquids from canned vegetables were used as medium in comparison with brain broth and hormone broth. The extract from white potato was found equal to the best medium for promoting growth. The liquid from cans of peas, corn and salmon gave lesser growth, while that from spinach gave growth only after being neutralized.

The reaction in cans of asparagus, string beans, beets, pumpkin, and spinach probably explains the irregularity of toxic production so frequently noted in these foods.

The reaction in certain canned vegetables is greatly affected by the quality of the material put in the cans. Experiments with spinach show that a small amount of rotted material will reduce the acidity to a point at which *Clostridium botulinum* can grow and develop a toxin.

AUTHOR'S SUMMARY.

STANDARDIZATION OF TUBERCULIN. ESMOND R. LONG, J. Infect. Dis. **37**:368 (Oct.) 1925.

Methods used at present in the standardization of tuberculin may be grouped as (1) those based on the action of tuberculin on the hypersensitive tuberculous animal, and (2) those based on the interaction of tuberculin and serum antibodies in the serum of a tuberculous animal. While each of the methods within these groups has its individual advantages, the disadvantages in all are great. The method in which the minimum lethal dose for a tuberculous guinea-pig is determined is altogether too gross, too many unknown factors being concerned. The method in which the ultimate dilution giving a cutaneous test in a tuberculous guinea-pig is determined is unreliable because of the wide individual variation in skin reaction capacity in tuberculous guinea-pigs of the same series.

The precipitin and fixation reactions between tuberculin and the serum of a tuberculous horse or horse inoculated with dead tubercle bacilli are unsuitable as standardizing methods because we have no assurance that the substance in raw tuberculin which reacts with the serum of the inoculated horse is the active principle of tuberculin. In fact, there is much evidence that it is not, and that the reaction which does take place between raw tuberculin and such serum is the result of interaction between serum antibodies and bacillary substance in the tuberculin, which cannot be properly called the active principle, that is to say, the substance which elicits the tuberculin reaction.

A method is proposed which is based on the hypersensitiveness of the spermatocytes of the tuberculous guinea-pig to the action of tuberculin. The spermatocyte reaction (previously reported as the testicle reaction) is delicate, and when carried out in the manner described above is of greater constancy

and reliability than the other methods based on hypersensitiveness of the tuberculous guinea-pig, viz., the minimum lethal dose and the cutaneous test methods. Necrosis and subsequent absorption of the spermatocytes is used as the basis for recognizing a positive reaction, and the limiting dilution at which this is observed under the conditions outlined above is considered to represent one unit of tuberculin.

AUTHOR'S SUMMARY.

ISOLATION OF BACTERIOPHAGE FREE FROM BACTERIAL PROTEINS. LLOYD ARNOLD and EMIL WEISS, J. Infect. Dis. **37**:411, 1925.

It was not possible to absorb completely the dissolved antigenic bacterial proteins from bacteriophage with the homologous bacterial antiserum.

A filtrate free from antigenic bacterial proteins but containing a strong lytic substance could be prepared from a bacteriophage in the following manner: (1) precipitating with sodium sulphate in 14 per cent concentration; the addition of antibacterial or normal serum hastens the reaction; (2) digesting bacteriophage with trypsin for forty-eight hours. Antibacteriophagic serum free from bacterial protein antibodies has been obtained by these methods. The only antibodies produced by bacteriophage are neutralizing bodies or antilysins. There are no complement-fixing antibodies present in antibacteriophage serum.

AUTHORS' SUMMARY.

THE SIGNIFICANCE OF HAEMIC PLASMA CELLS IN VARIOUS INFECTIVE CONDITIONS. R. A. HICKLING, J. Hyg. **24**:120, 1925.

The blood picture in rubella is characterized by the presence of numerous plasma and Türck cells and by the absence of toxic changes in the neutrophil leukocytes. Plasma cells occur also in scarlatina and in measles but with less regularity and, as a rule, in smaller numbers, but these diseases are always associated with "toxic" changes in the neutrophilic cells.

ARTHUR LOCKE.

THE SEROLOGY OF THE BOVINE TYPE OF THE TUBERCLE BACILLUS. W. M. CUMMING, Am. Rev. Tuberc. **7**:105, 1925.

Tubercle bacilli of the human and bovine type cannot be differentiated by agglutination or by absorption of specific agglutinins.

MAX PINNER.

THE ATTENUATION OF TUBERCLE BACILLI IN INCUBATED TUBERCULOUS TISSUES. G. B. WEBB, C. T. RYDER and G. B. GILBERT, Am. Rev. Tuberc. **10**:242, 1925.

Tuberculous lymph nodes which after ten days of incubation were implanted into seven guinea-pigs caused chronic tuberculosis in two animals; one, killed 570 days after the implantation, was free from tuberculosis. The remaining four guinea-pigs, which showed no sign of tuberculosis, were infected with virulent tubercle bacilli 130 days after they had received the tuberculous nodes. They all died of generalized tuberculosis, the average duration of the disease being 107 days, whereas normal controls lived only an average of 66 days following the infection. Tuberculous liver and spleen from guinea-pigs with chronic tuberculosis planted into guinea-pigs resulted in generalized, slow tuberculosis. Tissues from guinea-pigs with acute tuberculosis caused a much more rapidly progressing disease.

MAX PINNER.

THE INFLUENCE OF IRON ON THE GROWTH OF THE TUBERCLE BACILLUS UPON GLYCERINATED BEEF BROTH. R. R. HENLEY, Am. Rev. Tuberc. **10**:246, 1925.

After from eight to twelve weeks' incubation, the weights of pellicles of *B. tuberculosis,* human type, from glycerinated beef broth, which contained 20 mg. of ferric sulphate per hundred cubic centimeters, averaged 41 per cent more than the weights of pellicles from control broths which contained no added iron.

The p_H of the mediums had no noticeable effect on the growth.

The most favorable concentration of iron appeared to be from 0.01 to 0.03 Gm. of ferric sulphate per hundred cubic centimeters.

In general form the reaction curves of the control cultures resembled that regarded by Smith as characteristic of the human type of bacteria, and the reaction curve of the iron cultures resembled, at least for the greater part of the period of cultivation, that regarded by Smith as characteristic of the bovine type.

MAX PINNER.

AN INVESTIGATION OF THE ACID-FASTNESS OF TUBERCLE BACILLI. B. SUYENAGA, Am. Rev. Tuberc. **10**:260, 1925.

A strain of tubercle bacilli, Kl, isolated by Koch in or before 1888, was markedly reduced in its acid-fastness by numerous transfers. On non-nutrient medium and on an ameba medium the strain practically lost its acid-fastness; but even on these mediums the bacilli may again become acid-fast. The isolation of a non-acid strain from Kl was not possible.

MAX PINNER.

STUDIES ON THE ETIOLOGY OF JAGZIEKTE. I. THE PRIMARY LESIONS. E. V. COWDRY, J. Exper. Med. **42**:323, 1925.

The lungs of South African sheep, in a district in which jagziekte is appearing sporadically, differ from those of normal American sheep. Their structure is in general variable. They are more subject to the action of bacteria, demonstrable histologically, and to the effect of inhaled foreign material. The most significant difference, however, centers in the interalveolar tissue, which, in about 33 per cent of the animals is definitely thickened beyond the range of variation in this direction observed in American sheep. The thickenings occur in localized areas several millimeters in diameter. They begin with engorgement of the alveolar capillaries and accumulation of macrophages and of lymphocytes. Many of the macrophages pass into the alveolar lumina and assume the appearance of typical epithelioid cells.

STUDY OF A HEMOLYTIC PROTEUS BACILLUS. B. S. KLINE, Am. J. Hyg. **5**:656, 1925.

A proteus bacillus highly pathogenic for rabbits was isolated forty-eight hours postmortem in a case of severe anemia with clinical manifestations of pernicious anemia. The organism possessed great hemolytic power. The blood picture of eighteen inoculated animals was studied, the smears showing a moderate number of nucleated red blood cells, usually within forty-eight hours. Megaloblasts were also occasionally seen. Animals inoculated over a period of a few weeks developed a siderosis which was more marked in the spleen and bone marrow than in the liver. The bone marrow in the majority of the inoculated animals was hyperplastic.

E. E. ECKER.

PROTEUS HEMOTOXIN. E. E. ECKER and H. H. BRITTINGHAM, Am. J. Hyg. **5**:662, 1925.

The principal organism studied was the proteus isolated by B. S. Kline from human bone marrow. The hemotoxin was produced in broth and in synthetic medium cultures. The toxin rapidly hemolyzed human, sheep, dog, cat, guinea-pig and rat erythrocytes. The production of the hemotoxin varied with the strain employed. The hemotoxin was independent of the life of the organism, for the cultures remained toxic after cell death. The hemotoxin passed through a Berkefeld N candle. The hemotoxin was found to be thermolabile, and no "Koch gift" was obtained. Witte peptone in certain concentrations inhibited its action. Ultraviolet light retarded its power, depending on distance and length of exposure. Normal rabbit serums, if given sufficient time to act on the toxin, prior to the addition of corpuscles, will protect. Antitoxic (rabbit) serums, however, demonstrated a definite neutralizing power, immediately following its mixture with the hemotoxin. Under similar conditions normal rabbit serum failed to protect. The antihemotoxin did not protect against tetanolysin.

E. E. ECKER.

THE TRANSMISSIBLE BACTERIAL LYSIN AND ITS ACTION ON DEAD BACTERIA. F. W. TWORT, Lancet **2**:642, 1925.

Twort's experiments show that lysin will act on both dead and living bacteria, but is produced or possibly activated only in the presence of the living.

NASAL GRANULOMA IN CATTLE. V. KRISHNAMURTI AYYAR, Memoirs of the Department of Agriculture in India **3**:159, 1925.

There exists a widespread disease condition among cattle in the Madras Presidency and some other parts of India characterized by the development of chronic granulomatous formations on the nasal mucous membrane.

The disease appears to be of an infective origin.

Clinically, the disease is manifested by a snoring noise due to the obstruction of the nasal passages, and this symptom is aggravated by any condition which causes increased respiration. The disease is seldom fatal.

Histologically, the lesion resembles closely that of *Actinomycosis bovis*, and in the tissue follicles composed of connective tissue elements, one can readily demonstrate granules almost similar in appearance and texture to the so-called "ray-fungus" of actinomycosis.

ISOLATED TRICHOMYCOSIS OF THE CENTRAL NERVOUS SYSTEM. VICTOR JANUSZ, Trav. d'Inst. d'anat. path. d. Univ. de Pologne **1**:466, 1925.

The morphology of the parasitic fungi and the pathogenesis of the diseases due to them form a most interesting chapter in medicine. Little attention has been paid by clinicians to the mycoses other than actinomycosis. The pathologic conditions caused by *Trichomycetes* may be classified according to the location: trichomycosis of the mouth and larynx, of the lungs, of the digestive canal, of the skin. Trichomycosis of the nervous system is little known; a few cases have been described in the literature.

Most of the lesions in the nervous system are secondary. In a woman, aged 24, a tumor of the base of the brain was diagnosed. Her sickness began nine months before, with headache on the left side and vertigo, becoming worse after a delivery, with left ptosis, frequent loss of consciousness and symptoms

of meningitis. At necropsy, the dura, was found tightly stretched, the pia and brain substance congested and edematous. At the base of the brain, to the left of the sella turcica, there was an elevation in the dura, the size of a small egg, yellow and firm, resembling a fibroma. Histologic examination revealed a compact mass of filaments, surrounded by a zone of chronic inflammation, apparently a granuloma containing the mycelium of *Streptothrix*.

The mode of entrance of the organism could not be determined. Usually it is through the mouth, which was unaltered in this case. The nasal passages may also serve as a portal of entry. As no source of infection was found elsewhere in the body, the process was regarded as primary in the brain.

At neropsy, trichomycosis resembles the lesions of tuberculosis and tertiary syphilis closely, and can be distinguished only by microscopic examination. One must differentiate it also from the "senile plaques," the anatomic cause of presbiophrenia. Since the finding of mycelium in the brain is so rarely reported, and the condition so easily confused with the diseases mentioned, one should bear in mind the possibility of this infection in cases of latent sepsis.

B. R. Lovett.

Spirochetes in Chancroid. Hudelo and Rabut, Presse méd. **33**:1153, 1925.

Hudelo and Rabut noted coexistence of syphilitic infection in one of every seven in 173 patients with chancroid. They emphasize that association of Ducrey's bacillus with the spirochete of syphilis may not be detected for two months, since the incubation period of the latter is in certain cases prolonged, and a positive Wassermann reaction may not appear till late.

Pneumococcus Types and Prognosis in Pneumonia Crouposa. S. Christensen, Acta path. et microbiol. Scandinav. **2**:1, 1925.

The course of pneumonia does not seem to present variations ascribable to the types of pneumococci.

On the Miliary Papules of Yaws. Y. Ikegami, Acta dermat. **6**:509, 1925.

The eruption of yaws in the secondary stage takes the form of large vegetating papules. Six cases of miliary frambesides are described. They appear as papular or pustular follicular growths, disseminated or in groups. The Wassermann reaction was positive in three cases, and the growths were healed by arsphenamine. Histologically the inflammatory process consists of lymphocytes mingled with plasma cells and fibroblasts, and sometimes giant cells. Hyperkeratosis also occurs. The changes are therefore somewhat analogous to those of miliary syphilids. All the patients except one were children.

B. R. Lovett.

Compared Biology of Tubercle Bacilli in the Organism and in Culture Medium. E. Grasset, Rev. méd. de la Suisse Rom. **45**:520, 1925.

The study of different forms of the tuberculosis organism in many different culture mediums reveal corresponding differences in morphology and staining qualities. These indicate the need for developing more comprehensive methods for the recognition and isolation of the tubercle bacillus.

G. B. Rhodes.

CONTRIBUTION TO THE KNOWLEDGE OF THE THYROID CHANGES IN HEREDITARY SYPHILIS. ELISA MORELLI, Boll. d. Inst. sieroterapico Milanese **4**:215, 1925.

In early hereditary syphilis the thyroid shows hyperplasia and anomalous connective tissue distribution, unusual structural arrangement, degeneration of the epithelium and abnormal colloid formation. In later syphilis, altered structure but not hyperplasia of the connective tissue occurs, and evidence of a disturbed hypersecretion, a plasma transudate instead of a true colloid. In children with a positive Wassermann reaction but no clinical or anatomic signs of syphilis, necropsies after death by athrepsia reveal few distinctive changes except inconstant increase of connective tissue.

E. B. PERRY.

THE INFLUENCE OF TEMPERATURE ON THE TRANSFORMATION OF PARATUBERCULOSIS BACILLI INTO TUBERCULOSIS BACILLI. FRANCESCO SANFELICE, Boll. d. Inst. sieroterapico Milanese **4**:226, 1925.

Paratuberculosis bacilli grown at body temperature for a long time developed pathogenic properties and produced typical tuberculosis lesions in animals that had received injections. Acid-fast streptothrix injected intravenously into rabbits may be recovered alive and virulent from the urine, together with paratuberculosis bacilli which are transformed from the streptothrix by the action of the organism. Paratuberculosis bacilli constantly appear in the urine from patients with pulmonary or renal tuberculosis, but are infrequent in other patients or in normal persons.

E. B. PERRY.

THE DIFFERENT PHASES OF AUTOLYSIS OF B. ANTHRACIS. J. LEMOS MONTEIRO, Mem. do Inst. de Butantan **2**:95, 1925.

In gelatin cultures of *B. anthracis* the author has already demonstrated a lytic principle acting on bacilli but not on spores. By emulsifying and staining the cultures, the author has been able to follow the phases of autolysis from one day to several months. From the sixteenth to the ninetieth day the appearance is that of a culture acted on by bacteriophage, with accumulating cellular débris. On the one hundred and fifteenth day, the bacilli and débris disappear suddenly, and their place is taken by numbers of spores. The author thinks that the cellular débris may give birth to the spores when the lysin begins to menace the life of the race. Germs incapable of forming spores may be entirely destroyed, or their débris may give rise to the secondary forms that have been described by several authors as arising in emulsions kept in the laboratory. The nature of the lytic principle, certainly important in immunity, remains in the realm of hypothesis.

B. R. LOVETT.

IMMUNIZATION BY MOUTH AGAINST THE BACILLUS OF SHIGA. CONTRIBUTION TO THE STUDY OF THE MECHANISM OF IMMUNITY. EDUARDO VAZ, Mem. do Inst. de Butantan **2**:99, 1925.

The author discusses the theory of general immunity of local origin. With a strain of Shiga bacilli of low toxic and high antigenic power, rabbits were immunized by giving three or four increasing doses of dead bacilli orally. Their immunity was then tested against infection by oral, subcutaneous, and intravenous routes. The neutralizing and agglutinating power of the animals' serum was also tested. The author reached the conclusion that one can

immunize rabbits to the Shiga bacillus by the oral route. Many die of intoxication during the process, depending on the size of the dose and the strain of organism. With two strains, complete immunity was obtained to oral, subcutaneous and intravenous infection. In all cases in which there was immunity, the serum had antitoxic but not agglutinating power. When there was no antitoxic power, there was no immunity either local or general. Immunization by the oral route produces a general immunity.

B. R. Lovett.

The Epidemic Nature of Anterior Poliomyelitis: Spontaneous Transmission from Monkeys to Guinea-Pigs. Hugo Picard, Ztschr. f. Hyg. u. Infectionskr. **105**:307, 1925.

Picard confirms Neustädter's observation of a spontaneous transmission of experimental poliomyelitis of monkeys to guinea-pigs kept in cages close to those of the diseased monkeys.

W. Ophüls.

The Question of the Influence of Radiant Energy on the Growth of Tubercle Bacilli in Vitro. M. Friedland, Centralbl. f. Bacteriol., Parasitenk. u. Infectionskr. I. O. **95**:404, 1925.

The investigations show that of all kinds of radiant energy used, the sun's rays have the strongest bactericidal effect on tubercle bacilli in vitro, with the artificial light of the arc lamp and mercury quartz lamp as a close competitor. White light works best, but the single divisions of the spectrum probably also have some power. Of the colored rays, the green exercise the strongest inhibition to the growth of tubercle bacilli. The bactericidal effect depends chiefly on direct action on the bacteria, but somewhat also on changes in the nutrient medium. Roentgen rays and the beta and gamma rays of radium have no effect on tubercle bacilli in vitro.

B. R. Lovett.

Activity of Bacteriophage in the Paratyphoid Group. F. Breinl and F. Hoder, Centralbl. f. Bakteriol., Parasitenk. u. Infektionskr. I. O. **96**:1, 1925.

The dissolution of bacteria is only one special and extreme case of the activity of bacteriophage. A large part of the organisms exposed to bacteriophage undergo changes in cultural and serologic reactions and in their susceptibility to bacteriophage. In most cases the variations are not stable, but the longer the bacteriophage acts on the organisms, the nearer they approach to a single form. In the case of paratyphoid bacilli, transformation was effected of several variations into a single, stable form that culturally and serologically did not differ greatly from the original organisms. All strains tend to revert, and so it may be that not the variations themselves but the reversions from them, lead to the single stable form. The same variations were produced through mutations from aging broth cultures. This fact supports the theory that bacteriophage activity is closely related to mutation.

S. A. Levinson.

Allergy, Primary Lesions and Miliary Tuberculosis. R. Korteweg and E. Loeffler, Frankfurt. Ztschr. f. Path. **31**:136, 1925.

This is an interesting experimental investigation in which the writers have endeavored to establish the relationship of miliary tuberculosis to allergy. They

first experimented on ten subcutaneously inoculated animals to determine whether the kidney and bone marrow (which are commonly supposed to escape infection under these conditions in guinea-pigs) would show tubercles. In four of ten guinea-pigs lesions were produced in the kidney, showing that a hematogenous infection may follow subcutaneous inoculation. They then carried out two series of experiments in animals previously inoculated subcutaneously or intradermally. In one set they injected 11,000,000 tubercle bacilli into the left side of the heart, which was approached through the left lung. The bacilli were in the finest possible suspension. A bacillemia resulted, with an occasional slight lesion, but no general miliary tuberculosis. In the second series they injected from 0.2 to 0.5 cc. of a suspension in which the bacilli were in coarse, visible clumps and masses. Here they produced typical miliary tuberculosis.

They conclude that the kidney and bone marrow may become hematogenously infected following subcutaneous inoculation into guinea-pigs. One can produce a miliary tuberculosis only under conditions of allergy, otherwise "primary lesions" ("Primäraffekte") and not miliary tubercules result. Injections of tubercle bacilli in fine suspension into the blood of guinea-pigs produces bacillemia, without miliary tuberculosis. Miliary tuberculosis results only after the intravenous injection of coarse, visible suspensions of tubercle bacilli. There is a strong tendency to healing in the experimental miliary tuberculosis of guinea-pigs. The histologic picture and development of the primary lesion and of the miliary tubercle differ throughout their entire course. Writers frequently speak of "miliary tubercles" when they mean "primary lesions."

FOOT.

EXPERIMENTAL STUDIES ON THE ETIOLOGY OF LYMPHOGRANULOMA. A. GRUMBACH, Frankfurt. Ztschr. f. Path. **31**:530, 1925.

Grumbach has isolated an organism from six cases of Hodgkin's granuloma during the stage of acute exacerbation. He describes its bacteriologic peculiarities in detail, giving its cultural characteristics, morphology and tinctorial reactions. At first it is coccoid, then develops into a short, rod-shaped form, with irregular staining, not unlike *B. diphtheriae*, but definitely different from Hoffmann's and the forms classed as pseudodiphtheria organisms. In time it develops club-shaped, irregular forms and, after a month or two, branching ones.

Mice, rabbits, guinea-pigs and one monkey received injections with the organism. Irrespective of the method of inoculation, all developed after from four to six weeks a chronic interstitial pneumonitis with many eosinophil leukocytes and large cells with pale, vesicular nuclei. Cells resembling the Sternberg (Dorothy Reed) giant cell were also observed. The interstitial exudate caused a marked narrowing of the pulmonary alveoli and respiratory embarrassment. The regional lymph nodes became involved early, and the peribronchial connective tissue presented considerable thickening. The lesions were almost similar to those of Hodgkin's granuloma, and Grumbach concludes that the interstitial changes in the lung are due to involvement of the interalveolar lymphoid tissue. He admits that his experimental lesions differ in their primary site from those in human beings, and modestly makes no claim to having solved the problem.

FOOT.

ON DYSENTERY BACILLI WHICH DO NOT FERMENT MANNITE. I. TANAKA, Sc. Rep. Govt. Inst. Infect. Dis., Tokio **3**:1, 1924.

In a study of 106 strains of *B. dysenteriae* isolated from acute cases in Japan, Korea and Manchuria, the author found fifteen which differed from types previously described. They resemble the Shiga bacillus in their inability to ferment mannite, but show no kinship by agglutination reactions, in these reacting with serums immunized to the Flexner and Y strains. Two subtypes are found, one fermenting dextrose, levulose, galactose, mannose and arabinose, the other fermenting maltose in addition to these. The inability to ferment mannite is uninfluenced by prolonged cultivation and by attempts at habituation. Xylose is fermented by the second subgroup with red discoloration of the medium, but not by the first group. Organisms of the Schmitz (Funahashi and Nakamura) types likewise fail to ferment mannite, but show a striking contrast to the new strains and to the Shiga bacillus, in their ability to ferment rhamnose.

The author would place these various recent types as follows:

Group 1, fermenting dextrose, levulose, galactose, manose and arabinose; group 2, fermenting maltose in addition to the foregoing; group 3 (Funahashi and Nakamura), like the foregoing but not fermenting arabinose and fermenting rhamnose.

H. E. EGGERS.

THE SUBSTANCE PROMOTING THE GROWTH AND FERMENTATIVE ACTIVITY OF YEASTS. K. ANDO, Sc. Rep. Govt. Inst. Infect. Dis., Tokio **3**:17, 1924.

For promoting the rapid growth and fermentation of yeasts, among a considerable number of substances of diverse character the most striking results are obtained with Tsukie's vitamin B, with oryzanin and yeast substances ("Bios" and "Co-Enzyne") showing some but less effect. With oryzanin and the yeast substances this ability was lost only to a slight degree by heating to 140 C. for two hours. Such treatment has previously been recorded as destructive to antineuritic vitamin and further evidence of the lack of identity of this vitamin with yeast growth-promoting substance is afforded by treating yeast substances and oryzanin with tenth normal and fifth normal alkali at 100 C., again without impairment of growth-promoting power. Adsorption with fullers' earth likewise removes vitamin without impairing ability to promote yeast growth. Hence the author concludes that the growth-promoting and fermentation accelerating effects are unsuited to the qualitative determinations of the antineuritic properties of vitamin B.

H. E. EGGERS.

Immunology

CONTRIBUTION TO THE STUDY OF THE POISON OF SPIDERS. VITAL BRAZIL and J. VELLARD, Mem. do Inst. de Butantan **2**:5, 1925.

There are two types of spider poisons, the necrotic and the neurotoxic. Solutions of poisons from five different species were studied. The poisons of *Ctenus ferus, Ctenus nigriventer* and *Trechona venosa* are very active and affect the nervous system alone, causing convulsions and paralysis. The venom of *Nephila cruentata* has a weak and exclusively local action, while that of *Sycosa raptoria* also causes local necroses, but is very active. Potent and specific antiserums can be produced for the different venoms; these should be used in cases of intoxication. The poisons are resistant to low temperatures and chemical agents.

B. R. LOVETT.

ANTITETANUS IMMUNIZATION BY THE METHOD OF TOXOID-TOXIN. J. LEMOS MONTEIRO, Mem. do Inst. de Butantan **2**:85, 1925.

To obtain the transformation of toxin into toxoid without loss of antigenic power, the author uses 5 per cent of formol; after fifteen days, the attenuation is complete. Horses immunized by this method which after five or six injections do not have one unit of antitoxin in the serum should be rejected. When the serum contains one unit, the immunization is continued with toxin. This method is more rapid and subject to fewer accidents than the method with pure toxin preceded by injection of antitetanus serum. The methods are equivalent as to final dosage of serum.

B. R. LOVETT.

THE ANTIGENIC PROPERTY OF POLLENS. H. L. HUBER and K. K. KOESSLER, Arch. Int. Med. **36**:751, 1925.

If suitable procedures are followed, the antigenic property of pollens can be demonstrated in specifically sensitized animals by: (*a*) production of characteristic fatal anaphylactic phenomena; (*b*) positive uterine strip reaction; (*c*) positive bronchoconstriction and (*d*) production of specific antibodies giving precipitin reaction, complement fixation and passive sensitization.

The response of sensitized uterine strips to *Ambrosia trifida* and *Ambrosia elatior* and to *Helianthus annuus* is specific.

The demonstration of the antigenic property of pollens while not itself proving the anaphylactic nature of pollen disease is highly significant for this interpretation.

Zea mays pollen contains an oxytocic principle.

S. A. LEVINSON.

THE IMMUNOLOGICAL RELATIONSHIPS OF STREPTOCOCCUS VIRIDANS AND CERTAIN OF ITS CHEMICAL FRACTIONS. II. SEROLOGICAL REACTIONS OBTAINED WITH ANTINUCLEOPROTEIN SERA. REBECCA C. LANCEFIELD, J. Exper. Med. **42**:397, 1925.

The immunologic behavior of two cell constituents of nonhemolytic streptococci has been studied: (*a*) One, the so-called nucleoprotein, is relatively nonspecific and gives rise to an antibody which shows group reactions with nucleoproteins of related species. (*b*) The other is nonprotein by qualitative chemical tests. Preliminary chemical examination has indicated that it may be a carbohydrate. Although this substance is highly reactive with the specific antibodies produced by the intact bacterial cell, yet in its chemically purified condition it is probably nonantigenic. Specific serologic reactions with this substance are closely related to specific agglutination of the micro-organism.

The study of serums prepared by immunization with the chemically extracted protein has shown the presence of antibodies for nucleoproteins alone. No antibodies against the specific soluble substance have been found in these serums. The protein antibodies are little, if at all, concerned in causing agglutination. Precipitin tests, complement-fixation reactions and absorption experiments have been used to analyze the group relationships with the nucleoproteins of other species. The proteins of each species of gram-positive cocci studied were immunologically similar within the species and showed definite relationships to the proteins from related species. Proteins from bacteria of unrelated species did not react with antiserums against streptococcus protein.

Two distinct antibodies have been demonstrated in antiserums prepared against living bacteria. By prolonged immunization it was found possible to produce serum with a high content of protein as well as specific antibodies. With ordinary methods, however, the immune serum had a low content of relatively nonspecific protein antibodies but a high titer for specific antibodies. The specific antibodies were not reactive with proteins, but were active with high dilutions of the soluble specific substance and were responsible for the parallel specific agglutination. Absorption experiments showed that the two antibodies in antibacterial serums were immunologically distinct.

LOCAL IMMUNIZATION OF RABBITS TO CUTANEOUS INFECTION WITH STAPHYLOCOCCUS AUREUS. TRACY B. MALLORY and ALEXANDER MARBLE, J. Exper. Med. **42**:465, 1925.

Bacterial filtrates were prepared by the methods described by Besredka, but these never developed any specific growth inhibiting factors. Such filtrates produced a strictly local immunity of the areas of the skin infiltrated, but such protection was never greater than that produced with the broth from which they were prepared. This immunity was manifest within eight hours and persisted for at least fifteen days.

Transcutaneous treatment by moist dressings soaked in either filtrate or broth was entirely ineffective.

Sites of healed cutaneous lesions showed a strictly local and nonspecific immunity for a period of from five to six weeks.

Repeated intracutaneous infection with virulent staphylococci failed to produce a general cutaneous immunity.

AUTHOR'S SUMMARY.

THE SOLUBLE SPECIFIC SUBSTANCE OF A STRAIN OF FRIEDLÄNDER'S BACILLUS. PAPER 1. MICHAEL HEIDELBERGER, WALTHER F. GOEBEL and OSWALD T. AVERY, J. Exper. Med. **42**:701, 1925.

A method is given for the isolation of a specifically reacting nitrogen-free polysaccharide from the so-called E strain of Friedländer's bacillus. The properties of this polysaccharide are described.

AUTHORS' SUMMARY.

THE SOLUBLE SPECIFIC SUBSTANCE OF FRIEDLÄNDER'S BACILLUS. PAPER II. CHEMICAL AND IMMUNOLOGICAL RELATIONSHIPS OF PNEUMOCOCCUS TYPE II AND OF A STRAIN OF FRIEDLÄNDER'S BACILLUS. OSWALD T. AVERY, MICHAEL HEIDELBERGER and WALTHER F. GOEBEL, J. Exper. Med. **42**:709, 1925.

The chemical and immunologic properties of the soluble specific substances of a strain of Friedländer's bacillus and pneumococcus type 2 are described and correlated, and the serologic and antigenic similarity of these biologically unrelated organisms is discussed as an example of heterogenetic specificity among bacteria.

AUTHORS' SUMMARY.

THE SOLUBLE SPECIFIC SUBSTANCE OF PNEUMOCOCCUS. THIRD PAPER. MICHAEL HEIDELBERGER, WALTHER F. GOEBEL and OSWALD T. AVERY, J. Exper. Med. **42**:727, 1925.

Refinements in the methods for the isolation of the soluble specific substances of types 2 and 3 pneumococcus are described. These improvements

have resulted in the isolation of the end-products in a form free from nitrogen and of enhanced activity with immune serum.

The soluble specific substance of type 1 pneumococcus is described and shown to differ sharply from the corresponding substances of the other two types, each of which, in turn, differs from the other.

Progress is reported on the identification of the sugar units from which the polysaccharides are built up.

The evidence so far accumulated is believed to favor strongly the view that the polysaccharides isolated are the actual specific substances of pneumococcus.

AUTHORS' SUMMARY.

EFFECT OF HEMORRHAGE ON THE HEMOLYTIC TITRE OF THE SERUM OF RABBITS. JOHN MILLS, J. Path. & Bact. **28**:579, 1925.

A study was made of the effects of hemorrhage on the antibody titer of the serum of rabbits immunized against sheep corpuscles. Following immunization the rabbits were bled 5 cc. each on several successive days, the serum obtained and the hemolytic titer determined. When a number of samples had been obtained, the rabbits were subjected to a bleeding large enough to reduce the hemoglobin percentage to 50 per cent or less.

The author found a marked fall in the lytic power of the serum as a result of the bleeding. This fall ran parallel with the fall in percentage of hemoglobin. He concluded that either the body fluids which restore the blood volume to normal following hemorrhage contain no hemolysin or if they contain hemolysin, it is unable to pass the endothelium with the other constituents of the fluids.

During the period of recovery when the hemoglobin percentage was progressively increasing, there was an increase in the concentration of the hemolysin of the serum. The author does not believe this is an apparent increase due only to overdilution of the blood. In rabbits that were transfused during bleeding so that the blood-forming organs were not stimulated, the rise in the hemolysin curve was more marked than it was in the bleeding experiments. The rise is, therefore, not due to an increased activity of the blood-forming organs leading to a renewed production of antibody. The author believes that there is a tendency toward equilibrium of antibody in the blood. Following hemorrhage the tissue fluids probably contain excess antibody as compared with the blood. Equilibrium between blood and tissue fluids takes place slowly because the antibodies are held back by the endothelium.

ERNEST M. HALL.

A STUDY IN ORGAN SPECIFICITY. G. F. S. DAVIES, C. H. KELLAWAY and F. ELEANOR WILLIAMS, Australian J. Exper. Biol. M. Sc. **2**:117, 1925.

Extracts of the perfused liver and renal cortex of the cat can be distinguished by means of cross fixation and absorption experiments, though not by the anaphylactic reaction of the sensitive plain muscle of guinea-pigs. This last method readily distinguishes both extracts from the serum of the cat. A common antigen (or antigens) plays an important rôle in sensitization with these tissues.

AUTHORS' SUMMARY.

STANDARDIZATION OF TYPHOID VACCINE. JOSEPH W. SMITH, JR., J. Infect. Dis. **37**:385, 1925.

Evidence is presented that there is a basic error in the Wright method of standardizing vaccines, which is due to the loss of red blood cells. In the usual Wright preparation the cells are lost to a great degree; in the counting chamber or "wet Wright" to a less degree. The loss appears to be unavoidable by even the most painstaking technic, and is probably accounted for largely by sedimentation and adherence to walls of apparatus. Hemolysis probably plays a minor rôle.

Because of this loss of red blood cells, the ratio of cells to bacteria is not 5:x, but 2.5:x or 3:x. Consequently, when the ratio 5:x is employed, the value for x becomes very much too great. In other words, the bacterial content of the suspension is overrated. The suspension is therefore overdiluted, and as a result the final product contains only about one-half as many bacteria as it is thought to contain.

The counting chamber method of standardizing typhoid vaccine gives a count which is only half that obtained with Wright's method.

For purposes of accuracy and uniformity it seems advisable to adopt the counting chamber method of standardization and to revise the expression of dosage to accord with the new standards.

AUTHOR'S SUMMARY.

THE ISOLATION OF SUBSTANCES WITH IMMUNE PROPERTIES. ARTHUR LOCKE and EDWIN F. HIRSCH, J. Infect. Dis. **37**:449, 1925.

A method has been presented for the preparation of a highly purified hemolysin. Hemolysin is separated from amboceptor serum by selective adsorption on homologous erythrocytes. It is recovered through a destruction of the combining capacity of the erythrocyte for the bound hemolysin. This is accomplished by means of ether extraction. The procedure outlined permits hemolysin to be obtained in good yield and of a purity such that but 0.000,125 to 0.000,18 mg. of protein are associated with each hemolytic unit.

It is demonstrated that the failure of certain reported preparations of hemolysin to give a positive chemical test for the presence of protein is due to the lack of a sufficient delicacy in the tests employed. Qualitative tests are proposed which, under restricted conditions, permit the detection of protein in concentrations as low as 0.006 to 0.035 mg. per cubic centimeter.

The stroma-hemolysin combination is loosened and made easily dissociable when the lipins of the stroma are partially removed by ether extraction. This behavior is correlated with the shifting of the iso-electric point of the stroma from p_H 5 to p_H 7, approximately, when the lipins are so removed. It is suggested that while lipin-free stroma protein may be antigenic in the production of hemagglutinin, the antigenic entity in the production of hemolysin is probably the entire lipoprotein complex.

When erythrocytes are added to an homologous immune serum, the hemolysin of the serum becomes redistributed between the added cells and some component of the serum. This component is not present in normal serum. It is probably derived from the disintegration of the erythrocytes used in the immunization. It is suggested that the appearance of antibodies in the blood plasma follows the disintegration, by lysis and phagocytosis, of antigen already saturated with antibody by a primary process.

AUTHORS' SUMMARY.

BLOOD GROUPING IN TWINS. A. F. CANELLI, Clin. Pediat. **7**:385, 1925.

Canelli examined thirty-nine sets of twins from 8 days to 6 years old, and found that both of the univitelline twins were invariably of the same blood group. Four of the nonidentical twins were of different groups, including two of different sex. The majority of the twins were of Groups I and II of the Jansky classification.

J. A. M. A.

STUDIES ON THE NATURE OF THE IMMUNITY REACTION. I. AN EXPERIMENTAL STUDY OF PNEUMOCCOCAL IMMUNITY. R. R. ARMSTRONG, Proc. Roy Soc. **98**:525, 1925.

II. A COMPARISON OF THE ANTIGENIC PROPERTIES OF SENSITIZED AND RAW PNEUMOCOCCAL VACCINES. Ibid., p. 545.

Following the inoculation of rabbits with a single dose of killed pneumococci, all traces of natural protective power disappear from the serum. This continues for two or three days, depending on the size of the rabbit and the size of the dose. Then suddenly the serum is protective and increases rapidly in protective power to a maximum on the sixth day. The maximum is directly and closely proportional with the size of the vaccine dose, provided this is not too large and is injected at one time. A rapid fall in immunity occurs if the initial large dose of vaccine is followed on the fourth day by a second large dose. A high titer is, however, regained in forty-eight hours and persists.

The pneumococcus combines proportionally with its homologous protective antibodies to form a "sensitized" vaccine. On inoculation, a sensitized vaccine liberates the greater part of its charge of antibodies, rapidly conferring a slight degree of immunity, and afterward excites an active immunity in a manner comparable with untreated vaccine. Sensitization reduces the intensity and delays the immunity response, as compared with that following a like dose of untreated vaccine. These effects are also observed with separate administration of immunizing serum both before and after vaccine injection.

ARTHUR LOCKE.

THE INHIBITORY EFFECT OF BLOOD SERUM ON HEMOLYSIS, II. E. PONDER, Proc. Roy. Soc. B. **98**:484, 1925.

The inhibition of saponin hemolysis by added blood serum is probably due to the formation of a loose physical compound between the lysin and the serum proteins. The reaction is described by equations similar to adsorption equations.

ARTHUR LOCKE.

CUTANEOUS VACCINATION AND CUTANEOUS IMMUNITY IN ANTHRAX. A. P. NEWODOFF, Ann. de l'Inst. Pasteur **39**:888, 1925.

Immunity to virulent anthrax cultures given subcutaneously or by mouth in horses and cattle was observed from eleven days to eight months after cutaneous vaccination with attenuated cultures. A single vaccination on a scarified skin was sufficient to afford protection.

G. B. RHODES.

EXPERIMENTAL RESEARCH ON ANTHRAX. CHARLES HRUSKA, Ann. de l'Inst. Pasteur **39**:897, 1925.

Attenuated anthrax vaccines (vaccine 1 and 2) are found to vary in virulence. Their conservation in agar, broth, salt solution or in a dry state produces varying degrees of diminution of virulence. Preserved in a dry state the vaccines maintain their virulence most uniformly. In practicing vaccination the second vaccine should be sufficiently virulent, and in badly infected regions vaccines should be given twice a year, or if only once, a third inoculation of the second vaccine should be given.

G. B. RHODES.

CELLULAR RESPONSE AND PHAGOCYTOSIS IN NORMAL AND IMMUNIZED GUINEA-PIGS. S. METALNIKOO and K. TOUMANOFF, Ann. de l'Inst. Pasteur **39**:909, 1925.

Study of the character of peritoneal exudates in normal and immunized animals indicates that the white blood cells have become modified in the course of immunization. Leukocytic and phagocytic reactions begin sooner and are more intense in immune than in normal animals. Phagocytosis begins later and lasts longer in normal animals and the phagocytic index is higher, which is probably due to both the early disappearance of organisms and the part played by the fixed cells of the mesentery and the omentum in immunized animals.

G. B. RHODES.

THE REVERSE ANAPHYLAXIS AND THE CAROTAL [CAROTID] COMPLEX OF SYMPTOMS IN THEIR RELATION TO CHINA-INK. J. FORSMAN and T. SKOOG, Acta path. et microbiol. Scandinav. **2**:55, 1925.

Reverse anaphylaxis is used by Forsman to designate the reaction that develops from injections of antibodies into an animal that contains the corresponding antigen, e. g., rabbit serum, lytic for sheep corpuscles, in guinea-pigs as the guinea-pig contains in its organ antigenic substances with respect to this serum. The shock of reverse anaphylaxis is identical with typical anaphylactic shock. Injections of China ink have no influence on reverse shock, but they prevent the typical form of shock. In case small doses of rabbit serum, hemolytic for sheep corpuscles, are injected centripetally into the carotid, disturbances of equilibrium, circular and rotary movements of the body, exophthalmos and incoordinate movements of the eyes result; larger doses kill. The symptoms constitute the carotal [carotid] complex of the authors. Injections of China ink protect against this complex for twenty-four hours, and consequently the authors conclude that reverse anaphylactic shock and the carotid complex are different phenomena.

E. B. PERRY.

PRODUCTION OF HETEROGENIC ANTIBODY IN ANIMALS BELONGING TO THE GROUP OF THE "GUINEA-PIG TYPE." X. FRIDE, Arb. a. d. Microbiol. inst. d. Volksunterrichtskomissariats **1**:18, 1924.

Serum of animals of the "guinea-pig type" immunized with erythrocytes and organs rich in heterogenic antigen does not contain heterogenic hemolysin.

H. E. EGGERS.

NEUTRALIZATION OF ANAPHYLATOXIN BY ARSPHENAMINE IN CONNECTION WITH THE PATHOGENESIS OF FATAL CASES OF TRYPANOSOME INFECTION. O. DUKELSKY, Arb. a. d. Microbiol. Inst. d. Volksunterrichtskomissariats **1**:27, 1924.

Experiments showed that the addition of arsphenamine to anaphylatoxin in vitro neutralizes the latter. Since the symptoms of death in acute trypanosomiasis are suggestive of anaphylactic shock, it may be conjectured that arsphenamine may be used successfully in combating this.

H. E. EGGERS.

ON THE PLURALITY OF HETEROGENIC ANTIGEN. X. FRIDE, Arb. a. d. Microbiol. Inst. d. Volksunterrichtskomissariats **1**:43, 1924.

In the organs and in the nucleated red cells of animals of the "guinea-pig type" there exists along with the specific antigen, heterogenic antigens for animals of remote species. (*a*) The red cells of the turtle contain heterogenic antigens for the sheep and fowl. (*b*) The red cells of the fowl contain heterogenic antigens for the sheep and the turtle. (*c*) The red cells of the sheep contain heterogenic antigens for the fowl and the turtle. (*d*) Organs of animals of the "guinea-pig type" contain antigens for sheep, fowl and turtle.

No evidence of heterogeneous agglutinins was found in serum of rabbits immunized with antigens of the sort here described.

H. E. EGGERS.

Tumors

SPINDLE CELL SARCOMA OF THE HEART. C. S. BECK and H. S. THATCHER, Arch. Int. Med. **36**:830, 1925.

The primary growth was in the wall of the left auricle. The distribution of the metastases indicated that they were borne by the arterial blood stream. The absence of metastases in the liver and lungs excludes the tumors of the intestine as the primary focus. A thrombus in the left auricle formed on the sarcoma that had involved the endocardium.

S. A. LEVINSON.

EPITHELIOMA OF CAVITIES AND INTERNAL ORGANS OF THE HEAD AND NECK. A. C. BRODERS, Arch. Surg. **11**:43, 1925.

Epitheliomas are divided into eight groups according to location and into four groups according to the degree of malignancy. The latter is judged by an arbitrary standard of the amount of cell differentiation in the neoplasm. Three hundred and sixty-two cases are presented and tabulated according to age, sex, location, size, duration, operation, previous ulcer, crack or leukoplasia; syphilis, cell differentiation, metastases and postoperative results. These are then presented in summary.

N. ENZER.

INJURY INCLUDING IRRITATION AND CANCER. W. M. L. COPLIN, Arch. Surg. **11**:124, 1925.

This article reviews the problem of the etiology of cancer, and points out that the irritation theory has best stood the test of clinical investigations, statistical study and experimental research. He presents a long list of conditions which have preceded or have been concomitant with cancer. These may be divided into mechanical, chemical, radiant and chronic infections. A

latent period may occur between the injury or irritation and the onset of the tumor. Cancer produced by chronic irritation may exist for a long time, and give rise suddenly to invasive metastases, as in the case of creosote cancer reported by Cochran. He advises careful investigation in dermatoses as a possible precancerous stage. Persistent irritation establishes some cytologic change in the reacting elements which persist after the withdrawal of the initial irritant, and may be manifested by the development of malignancy at some remote period, such as seen in tar and smokers' cancer.

N. Enzer.

Primary Bilateral Carcinoma of the Fallopian Tube. J. O. Bower and J. H. Clark, Arch. Surg. **11**:586, 1925.

A review of the literature shows that ninety-three of the cases were unilateral and forty-three bilateral. Expansion of this growth occurs toward the lumen or the abdominal ostium. The lateral end closes early, but the uterine end remains patent. Dissemination occurs possibly in three directions, by rupture of the tube, by lymph drainage to the fundus of the uterus to the cervix and to the retroperitoneal glands. Direct implantation of the ovary may also occur. The uterine cornua were involved.

N. Enzer.

The Behavior of Mitoses in Precancerous Tissue and in Cancer and Its Importance in the Origin of Cancer. Helene Schuster, Trav. d'Inst. d'anat. path. d. Univ. de Pologne **1**:354, 1925.

Many hypotheses concerning the origin of malignant tumors regard changes in the mechanism of cell division as a cause. A tumor cell is one which has become malignant through an abnormal process of division and an abnormal content of chromatin. This malignancy is shown by boundless growth.

One finds in malignant tumors great variation in the karyokinetic process, which, however, might be a secondary result of the abnormal growth in the tumor. Therefore, to be of significance in the origin of the cancer, the variation must be found in the precancerous stage.

The process of mitosis in this stage was studied in tumors produced by painting the backs of white mice with tar. The growth was divided into four stages: hyperplasia, papilloma formation, precancer, and cancer. Normal mouse skin was used as a control. Mitotic figures in the first three stages were all found to be normal. In the fourth stage, the figures were normal in the differentiated epithelial cells, but there were many abnormal figures among the undifferentiated cells.

These investigations have therefore a negative result.

B. R. Lovett.

Tumours of the Testicle: The Teratoid Group. F. Gordon Bell, Brit. J. Surg. **13**:7, 1925.

The article is based on the study of fifty specimens of testicular tumors. The vast majority of these tumors fell into two main categories: (1) the teratoid group, (2) the germinal cell variety. The present paper deals only with the first group, which predominated to a marked degree, and is classified by the author into the following types: (1) typical tridermal teratoma, (2) the solid apparently homogeneous tumor containing heterologous elements, (3) mesoblastic overgrowth, (4) hypoblastic overgrowth, (5) epiblastic overgrowth. Cartilage, smooth muscle and lymphoid tissue were the most frequent mesoblastic derivatives encountered. Thyroid tissue was present in three specimens,

and one contained adenomatous tissue resembling a cystic goiter. The essentially malignant character of these tumors, particularly of the hypoblastic elements, is stressed. One dermoid cyst of the human testicle was included in the series and another multilocular cyst containing hair and sebaceous material had been removed from a horse.

LAWRENCE JACQUES.

CHORIONEPITHELIOMA OF THE UTERUS. F. PAUL, Virchows Arch. f. path. Anat. **257**:675, 1925.

Complete hysterectomy was performed on a woman, aged 62, because of round cell sarcoma of the uterus, the diagnosis having been made by the microscopic examination of a bit of curetted material. Further details of the microscopic examination of the removed uterus or ovaries were not available to the author. The patient had had eight normal pregnancies and two abortions. The date of the last pregnancy was not known, but menopause had occurred ten years previous to the operation. The latter was followed by a large retroperitoneal metastasis, multiple metastases throughout the body, and death one year after hysterectomy. Histologic examination of the secondary tumors showed them to be typical chorionepithelioma, in which both Langhans cells and syncytium were present. Paul concludes that the primary tumor of the uterus was a chorionepithelioma which had originated in trophoblastic cells that had remained dormant but viable in the uterine wall.

O. T. SCHULTZ.

CHORIONEPITHELIOMA OF THE LIVER. E. CHRISTELLER and P. OPPENHEIMER, Virchows Arch. f. path. Anat. **257**:691, 1925.

A woman, aged 53, had had ten normal pregnancies, the last twelve years previous to admission. One year previously she had had a severe vaginal hemorrhage. At necropsy the uterus was found lined by a thin layer of endometrium, whose surface was covered by decidual tissue. The latter did not appear malignant. The liver contained multiple tumor nodules, which on microscopic examination proved to be chorionepithelioma. The ovaries, although senile, contained several large corpora lutea. No primary genital tumor could be found. Metastases were also present in the lungs and intestine. The authors were not able to decide whether the liver tumors had arisen from transplanted normal chorionic villi or from a primary chorionepithelioma which had disappeared. The twelve year period between the last pregnancy and the appearance of the chorionepithelioma is believed by the authors to have been only apparent; they think it probable that the vaginal hemorrhage one year before the development of the tumor may have been caused by an abortion or an hydatidiform mole.

O. T. SCHULTZ.

Medicolegal Pathology

MANGANESE POISONING AND ITS EFFECT ON THE CENTRAL NERVOUS SYSTEM. R. FINLEY GAYLE, J. A. M. A. **85**:2008, 1925.

Manganese, more often than is recognized, causes symptoms in workmen handling this ore.

That certain persons are not susceptible to the poisoning effects of manganese is demonstrated by the fact that many workmen in the plant have been in contact with manganese dust for several years, with no apparent ill effect.

Mental symptoms have been described by some investigators and denied by others. Mental changes were found in each of the patients of this series.

No record could be found of other investigators having detected manganese in the urine in clinical cases. Experimentally, it had been found in minute amounts. In this series, it was present in three of the five specimens of urine examined.

AUTHOR'S SUMMARY.

SADISTIC EROTIC MURDER. F. HARBITZ and R. VOGT, Norsk Mag. for Laegevidensk. **86**:1045, 1925.

This is a report of the murder of a woman with extreme mutilations of the body, by a man under the influence of alcohol.

MEDICOLEGAL INSTITUTE THROUGH FIFTEEN YEARS. J. FOG, Ugesk. f. Laeger **87**:1012, 1925.

This article gives a summary of the various phases of the work done by the Medicolegal Institute of the University in Copenhagen since the Institute has occupied a building of its own.

DEATH FROM ELECTRIC CURRENT. H. SCHRIDDE, Klin. Wchnschr. **4**:2143, 1925.

Schridde made necropsies on thirty-seven men who had been killed by electric currents of not more than 220 to 250 volts. He found in thirty-six of them typical signs of a "thymic constitution"; the lower extremities were long, the neck short, the skin frequently fine and pale and with only little hair, especially in the axillae, little or no beard, and a heterosexual or intersexual type of pubic hair. The thymus gland and spleen were enlarged. The only exception was one elderly man in poor general condition. Burns were not always present. In the positive cases they were on the left hand (shorter route to the heart) in 90 per cent. Therefore the old recommendation to keep one hand (the left) in the pocket while working was sensible. Edema of the lungs was present in twenty-one of his cases. The death in the remaining fifteen might be explained by fibrillation of the ventricle.

TOXICOLOGY OF HYDROGEN SULPHIDE. HOWAN W. HAGGARD, J. Ind. Hyg. **7**:113, 1925.

Hydrogen sulphide poisoning causes no distinctive anatomic changes. The necropsy findings in acutely fatal cases are simply those of asphyxia. In the occasional case in which death is delayed for a day or two, evidence of edema of the lungs may be found.

Neither hydrogen sulphide nor any combination of this substance with the blood pigment or blood alkali is ever found in the body at early necropsy after hydrogen sulphide poisoning. If there is a delay in performing the necropsy, however, blood pigment combined with hydrogen sulphide may be found in abundance. The bluish-green color of this sulphur compound is particularly noticeable in the vessels surrounding the intestines. The formation of sulphemoglobin or sulphmethemoglobin under these circumstances is entirely a postmortem change, and is not in any way indicative of a previous exposure to hydrogen sulphide. The author's conclusions follow:

Hydrogen sulphide is both extremely toxic and also irritant. It causes severe local irritation of the eyes and may induce pulmonary edema. The more severe irritant effects are, however, usually obscured by the symptoms of acute systemic poisoning.

Hydrogen sulphide is rapidly oxidized in the body. The oxidation products are nontoxic. In this, as in the intensity of toxicity, it compares with cyanides. Inhaled hydrogen sulphide forms no combination with, nor does it in any way alter, the hemoglobin of the blood.

In acute poisoning death results from respiratory failure. With concentrations below 0.1 per cent, respiration is little affected; with concentrations of 0.1 to 0.2 per cent, severe hyperpnea is induced and this terminates in apnea vera; with concentrations over 0.2 per cent, respiration is paralyzed without a preliminary hyperpnea. Breathing may be resumed spontaneously after the apnea but never (unless assisted by artificial respiration) after the paralytic form of respiratory failure.

The heart continues to beat for several minutes after respiratory failure. During this time manual artificial respiration (Schäfer method) will reestablish breathing. Inhalation of oxygen containing 5 per cent carbon dioxide is beneficial during and for a short time after the period of artificial respiration.

The prophylaxis of hydrogen sulphide poisoning consists in wearing suitable masks and goggles or keeping the contamination of the air at a low level by means of forced ventilation.

Technical

A Simple and Sensitive Modification of the Wassermann Test. E. F. Ecker, J. Lab. & Clin. Med. **11**:76, 1925.

The modification described is based on the well-known fact that an excess of amboceptor (5 units) will eliminate the rôle played by the natural antisheep amboceptor present in the patient's serum. It also allows a sharp complement titration, which is done in a 1:30 dilution. In the test, however, the pooled complement is added from the 1:10 dilution. The amboceptor is glycerolated (50 per cent), and the cell suspension is standardized by Sahli's method or by Hopkins tube. The antigen is the acetone insoluble fraction. To prepare, extract 30 Gm. of beef heart powder in an Erlenmeyer flask with attached coil-condenser for three or four hours, using chemically pure acetone (200 cc.). Chill the mixture in the icebox, filter and dry the residue until the acetone is evaporated. Reextract the residue in the same apparatus with 95 to 100 per cent methyl alcohol (200 cc.) for three or four hours. Evaporate down to 90 cc. The antigen may be cholesterolized with 0.2 per cent cholesterol if so desired. Titrate with strong, weak and negative serums, titration with a weak serum being important. Citron's three tube method is employed and over-night fixation with 2 units of complement. Spinal fluids can be employed in doses up to 1 cc., and for quantitative work the serum of the patient is diluted. The reaction is simple, reliable and specific. No false reactions have been obtained in cases of scarlet fever, malaria or pregnancy.

E. E. Ecker.

The Diameter of the Red Blood Cells in the Differentiation of Anemias. L. C. Grosh and J. L. Stifel, Arch. Int. Med. **36**:874, 1925.

A technic is described for the measurement of the diameter of red blood cells and for the construction of diameter curves which is sufficiently accurate for clinical purposes and sufficiently simple to be used in a routine manner in examining any questionable blood specimen.

The diameter curves are of value in the differentiation of Addison's anemia in all its stages and of secondary anemia.

S. A. Levinson.

CLINICAL VALUE OF SOME RECENT TESTS FOR LIVER FUNCTION. H. F. SHATTUCK, J. C. BROWNE and M. PRESTON, Am. J. M. Sc. **170**:510, 1925.

The icterus index is the most useful functional liver test.

ICTERUS INDEX. J. V. BARRON, E. L. ARMSTRONG and W. H. OLDS, Am. J. M. Sc. **170**:519, 1925.

The icterus index is simple, accurate and without danger. It measures the bilirubin in the blood.

THE VAN DEN BERGH TEST FOR ICTERUS IN THE BLOOD OF INFANTS. C. G. GRULEE and ANNETTE MEBANE, Am. J. Dis. Child. **30**:219, 1925.

After reviewing the literature, Grulee and Bebane detail the test which is in reality a diazo reaction on the blood serum.

They have divided their cases in five groups. In the icterus neonatorum group there were five cases in which umbilical cord blood was used, and seven in which blood from the sinus was taken. In each case the indirect reaction was obtained. In three cases of icterus complicating acute respiratory infections, the indirect reaction was obtained. In one case of icterus resulting from the administration of neo-arsphenamine the indirect reaction was obtained. In two cases of acute catarrhal jaundice the reaction was indirect in both. In one case of obstructive jaundice, probably due to the congenital atresia of the bile ducts, the reaction was twice indirect and once direct.

They conclude that the evidence in this series is such as to raise a doubt as to the value of the van den Bergh reaction as a method of differentiating between obstructive and nonobstructive types of jaundice in infants and young children.

AUTHORS' SUMMARY.

STUDIES OF ACIDOSIS. XXI. THE COLORIMETRIC DETERMINATION OF THE p_H OF URINE. A. B. HASTINGS, J. SENDROY, JR., and W. ROBSON, J. Biol. Chem. **65**:381, 1925.

A technic is described for the colorimetric determination of urine p_H, using bicolor standards and empirical corrections for dilution errors. The values agree closely with corresponding values obtained electrometrically.

ARTHUR LOCKE.

A MORE SPECIFIC REAGENT FOR THE DETERMINATION OF SUGAR IN URINE. J. B. SUMNER, J. Biol. Chem. **65**:393, 1925. Cf. ibid. **62**:287, 1924-1925.

The excessive color values given by dinitrosalicylic acid with normal urine are corrected in a modified method in which phenol and sodium bisulphite are added to the reagent.

ARTHUR LOCKE.

A METHOD FOR THE DETERMINATION OF TOTAL SULFATES IN TISSUES. W. DENIS and S. LECHE, J. Biol. Chem. **65**:561, 1925.

The method consists in a digestion of the minced tissues by autoclaving with dilute hydrochloric acid, centrifugation to a clear solution, and precipitation of the sulphates therefrom with barium chloride.

ARTHUR LOCKE.

STOOL EXAMINATION FOR PROTOZOA IN ELEVEN HUNDRED INMATES OF A NEW YORK STATE INSTITUTION. WALTER S. THOMAS and E. A. BAUMGARTNER, J. A. M. A. **85**:1725, 1925.

In 1,122 inmates, 44.47 per cent showed intestinal protozoa on examination of a single stool specimen from each. There was evidence of cross infestation in the institution. The influence of age is not great except in the case of *Giardia lamblia*, in which the young persons are more often infested. *Chilomastix mesnili* was the organism most often found. *Endameba histolytica* was seen in only 1.07 per cent of the persons examined. Taking this low figure into consideration, together with the facts that the class of patients was one in which a high incidence might be expected, that the patients were all confined in an institution where cross infestation takes place and that none of the 1.07 per cent with *Endameba histolytica* had at any time shown any evidence of amebic disease, the authors feel justified in believing that *Endameba histolytica* plays only an insignificant rôle in the production of disease in New York State.

THE DIAGNOSTIC VALUE OF CHOLESTEREMIA DURING PREGNANCY IN TUBERCULOUS WOMEN. M. SALOMON and DEPOTTER, Compt. rend. Soc. de biol. **43**:891, 1925.

The normal value for blood cholesterol in women during the last month of pregnancy is about 250 mg. in 100 cc.; this hypercholesteremia usually persists for several weeks after delivery. In tuberculous women with active or advanced pulmonary lesions, only 209 mg. were found; in nonprogressive cases 233 mg. was the average. Immediately after delivery the cholesterol dropped markedly in progressive cases, whereas in stationary forms the level reached before delivery is maintained better. Hypocholesteremia after delivery constitutes a grave prognostic sign in tuberculous women.

MAX PINNER.

THE SEDIMENTATION TEST. I. FREUCHEN, Hospitalstidende **68**:871, 1925.

Within certain limits the diameter of the tube is immaterial for the outcome of the sedimentation test. The reading is most instructive at the half hour and the hour. Freuchen found that ten drops of the 3.5 per cent sodium citrate solution gave the best results using a glass of 13 mm. diameter, of a capacity of 7.5 cc. The highest figure he obtained was in a man with pernicious anemia; the figure was 39.5 at the half hour and 42 at the full hour. In blood from twenty horses, tested minute by minute, the greatest differences between the sick and the well were observed at the eleventh minute, sedimentation occurring much more rapidly in horse blood than in human blood.

A MICROMETHOD FOR THE DETERMINATION OF PLASMA LABILITY. JAKOB WEGIERKO, Wien. klin. Wchnschr. **38**:932, 1925.

The results of flocculation tests of 100 specimens of blood support the general opinion that increased flocculability attends conditions with marked tissue destruction. Attention is called to the convenient method. Only 0.2 cc. of blood is needed. The citrated plasma, handled best with a Wright's pipet, is made into four different solutions with physiologic sodium chloride, heated in a water bath at 52 C. for three minutes, or at 54 C. if necessary. The flocculation is then read from + to ++++, according to the number of dilutions showing change.

E. B. PERRY.

Society Transactions

PHILADELPHIA PATHOLOGICAL SOCIETY

Regular Meeting, Dec. 10, 1925

E. B. KRUMBHAAR, M.D., *President*

POSTPARTUM PNEUMOCOCCIC PERITONITIS. S. V. ELLSON.

Two cases of primary pneumococcus peritonitis are presented, both occurring in the puerperium, the first four and one-half weeks after delivery and the second case eight weeks after delivery. Both had a sudden onset and were rapidly fatal. Necropsy of each case showed generalized purulent peritonitis most marked in the pelvic region. No other focus of pneumococcus infection was found at necropsy. Cultures from each case gave a heavy growth of type I pneumococcus.

These two cases of pneumococcic peritonitis are remarkable in their similarity. They seem to establish this condition as a definite entity. This report seems justified, for a brief survey of the literature has failed to reveal any similar cases.

Primary pneumococcic peritonitis has received definite attention during the past ten to fifteen years. Our knowledge of the etiology of this condition has been greatly increased by the work of McCartney and Fraser. These authors claim that the primary variety (i. e., not secondary to another focus in the body, as pleura, lungs or joints) is limited to the female sex, and this peculiarity is explained by the fact that the infection of the peritoneum is from the exterior through the medium of the female genital tract.

We know this is definitely established in gonococcal infection, and Milcher has given strong evidence of it in some cases of tuberculous peritonitis. Further, the disease seems to start and be more extensive in the pelvic region, and no cases of primary pneumococcic peritonitis are reported in the male.

The disease occurs chiefly in children between the ages of 2 and 8 or 9 years, the incidence being greatest about the sixth year. This is explained by the fact that the patency of the female vagina is not definitely established until the second or third year. Until the seventh to eighth the vaginal secretion is alkaline in reaction, then changes to become acid.

The occurrence of primary pneumococcic peritonitis in adults is comparatively rare. In the two reported cases the question arises as to what influence the recent childbirth may have had. We know there is a greater susceptibility to infection on the part of the genital tract in the puerperium in other types of infection.

These cases add further proof that a primary pneumococcic peritonitis occurs through the female genital tract as a portal of entry, and that the adult uterus and tubes may under certain conditions become susceptible, a point which is well recognized in children.

PERIDUCTAL SARCOMA OF THE BREAST. BOWMAN C. CROWELL.

The case is one of sarcoma of the breast occurring in a woman, aged 52, who had been a widow for five years. She had a normal menstrual life and no children. One miscarriage during the third month of gestation occurred

sixteen or seventeen years before presentation. For between ten and fifteen years she had a movable, painless, walnut-sized nodule in the lower outer quadrant of the left breast, to which she paid no attention. At the time of her last menstrual period, April, 1925, enlargement of this nodule commenced, and continued until the time of her admission to the service of Dr. John Chalmers DaCosta at the Jefferson Hospital, Aug. 31, 1925. At this time the mass in the left breast was described as being the size of an orange. Left axillary and left posterior cervical lymph nodes were palpable. Amputation of the breast and dissection of the left axilla was performed by Dr. W. P. Hearn. Recovery from operation was uneventful.

The specimen as received at the laboratory consisted of the breast and the contents of the left axilla, together with some of the skin overlying the breast and including the nipple. There was marked retraction of the nipple. The mass in the breast was circumscribed and encapsulated, extending downward and outward from the region of the nipple. It measured 7 by 7 cm. and 3.5 cm. in depth. It was solid, pale with a distinctly slimy feel on the cut surface, appearing more gelatinous in some parts than in others. At the pole nearest the nipple there was a cyst about 2 cm. in diameter, into which protruded a papillary mass which almost completely filled this smooth-walled cyst. There was no evidence of infiltration of the surrounding tissue. A few lymph nodes were found in the axilla enlarged to about 1 cm. in diameter. These were pale, firm and homogeneous.

Microscopically, longitudinal and cross sections of ducts lined by low cuboidal epithelium were seen, the ducts being much compressed. About these the loose fibrillar periductal connective tissue constituted the rest of the tumor, giving the basic structure of the usual intracanalicular adenofibroma. This connective tissue appeared as a loose meshwork in most parts, the fibers being separated by a substance not stained by hematoxylin or eosin. The arrangement of these fibers conformed to no definite architectural arrangement. In many parts of the sections these fibers showed very large, deeply staining nuclei of a diffuse, blotchy nature. The character of the intercellular substance suggested the so-called myxomatous change. While this tumor showed no evidence of infiltrating surrounding structures, and while the axillary lymph nodes showed no metastasis (only a chronic inflammatory reaction), the unusually active growth of the connective tissue as manifested by the nuclear structures and the irregularity of the architecture of this tissue justify one in classifying it as an intracanalicular adenofibroma in which a sarcomatous change has supervened.

The type of tumor here presented is a well recognized one, but one that is relatively rarely encountered. While sarcoma of the breast of all types constitutes about 3 per cent of malignant tumors in that organ, the type here described forms but a small percentage of these.

Of 755 tumors of the breast examined in the laboratories of the Jefferson hospital during the past twenty-seven years, 485 (64 per cent) have been malignant, and of the latter, fifteen (3 per cent) have been diagnosed sarcoma. A recent review of these fifteen tumors shows only two of them of comparable histologic structure to the one here presented, but in neither of these was the clinical course the same.

– UNIQUE HEART ANOMALY: FREE FIBROUS CORD PASSING THROUGH THREE HEART CHAMBERS TO THE AORTA. J. L. GOFORTH.

This interesting necropsy finding from the laboratories of the Philadelphia General Hospital, department of pathology, is recorded primarily because it is unique.

The patient, a white woman, aged 23, came to necropsy with a clinical diagnosis of postpuerperal psychosis. The history, clinical course and other necropsy findings are of no consequence, and are omitted. According to Dr. J. F. Stauffer, of the Philadelphia General Hospital, on auscultation, there was a gallop rhythm, and at the apex a "sort of to-and-fro murmur which sounded like a cross between a friction rub and a murmur" was heard which could not be definitely timed because of tachycardia. Pericarditis was suspected.

The heart weighed 300 Gm., was of normal size and shape, and showed slight right-sided dilatation. The pericardium and epicardium were not remarkable. The coronary vessels were negative. The auricular and ventricular walls were of normal thickness, and the myocardium was of normal color and consistency. The endocardium and valves presented no organic lesions. The mitral valve, particularly the anterior leaflet, showed slight thickening along its line of closure, but was everywhere smooth and shining. The aortic cusps were not remarkable except as described.

Arising from the right auricular wall, 2 cm. from the annulus ovalis, a tiny, grayish-white, rounded, threadlike cord, 0.5 mm. in diameter, ran freely and unattached toward the partly patent foramen, and near the lower rim of the annulus ovalis, apparently obliquely pierced the interauricular wall. Attached to the annulus ovalis, inferior margin, left auricular wall, it traversed the left auricle, and, following the course of the blood flow, passed down through the mitral orifice well into the left ventricle. Here it turned, and, forming a parabola-like curve around the anterior mitral leaflet, proceeded toward the aortic valve. As it approached the anterior cusp, it pierced it perpendicularly and attached itself to the wall of the aorta 6 mm. beyond, thus virtually transfixing this cusp. The cord tended to increase in size as it progressed; in its course through the left auricle and ventricle, it increased from 0.6 mm. to 2 mm. in diameter; it was thickest in its curve around the mitral leaflet, reaching a diameter of 2.5 mm. in this section. As it approached the aorta it again became smaller, averaging not more than 0.5 mm. as it pierced the cusp. The entire cord was about 12 cm. long: 2 cm. from its origin in the right auricle to the foramen ovale; 5.5 cm. from the annulus ovalis, left auricle, to the curve in the left ventricle; 4 cm. from the curve to the aortic valve, and 6 mm. from the cusp to the aorta. It was rounded throughout its course, and on palpation was firm and solid, but easily pliable.

Hematoxylin and eosin, Mallory's aniline blue stain for fibrous tissue, and Weigert's elastic-fiber-stain preparations of both transversely and longitudinally cut sections, taken from blocks at different levels of the thickest portion of the cord, showed closely packed bundles of wavy collagenous fibrils running longitudinally in the main, although a few took a circular course. An occasional flattened endothelial cell was observed on the outer surface. Transverse sections of the portion of the cord that had pierced the aortic cusp showed essentially the same picture; the dense fibrous tissue here tended to arrange itself in a sort of laminated fashion. In no section was there any evidence of cardiac or smooth muscle tissue, elastic tissue, or Purkinjes' fibers. Microscopically, the cord was composed of dense fibrous tissue, and was covered by a thin endothelial membrane.

The points of attachment and course of the cord suggest that it might have formed during fetal life in association with some irregularity in the fetal circulation. There was nothing in the structure of the cord to indicate definitely its formation embryologically, yet its origin as a developmental anomaly seems the most probable.

CALCULUS IN THE KIDNEY PELVIS OF THE BLACK HANDED SPIDER MONKEY (OEBUS APICULATUS). HERBERT FOX.

This specimen was a renal calculus in a monkey which recently came to necropsy at the Garden of the Philadelphia Zoological Society. It is not only the first calculus found in the urinary tract in 596 necropsies on primates, but appears to be the first case on record.

Urinary calculus is rare in wild animals, more common in domestic animals. Only eight cases have occurred among 8,000 specimens examined at the Zoological Garden. Of these animals, five were ungulates, two birds and one belonged to the carnivora.

The condition is commonest in *Herbivora*, especially in those with a single pyramid in the kidney, as in ungulates. Calculi in these animals are often large, but produce no marked inflammatory changes.

In the case reported, no symptoms were observed referable to the renal condition.

MICROSCOPIC PREPARATIONS MADE FROM SOME OF THE ORIGINAL TISSUE DESCRIBED BY THOMAS HODGKIN, 1832. HERBERT FOX (From the William Pepper Laboratory of Clinical Medicine, University of Pennsylvania).

There are three specimens remaining in the Museum of Guy's Hospital, London, from the original tissue used by Thomas Hodgkin in describing the condition to which Sir Samuel Wilks in 1865 gave the name "Hodgkin's Disease." Only three of the seven cases described by Hodgkin seem acceptable as representing the disease as we understand it today. Case 2 of his paper is represented in Guy's Museum by two specimens nos. 1523 and 4768, spleen and lymph nodes. The spleen and its attached nodes have been preserved very well. Microscopic sections made recently show a micro-anatomy that is typical of the disease, and this from tissue that was preserved in spirits eighty-two years and formalin fifteen years longer. Sections from the other two cases have not been preserved so well, and the diagnosis is not so satisfactorily determined today. By this observation it is evident that Hodgkin saw at least one case of malignant lymphogranuloma as we know it today.

HISTOLOGIC CHANGES BROUGHT ABOUT IN CASES OF EXOPHTHALMIC GOITER BY THE ADMINISTRATION OF IODINE. WILLIAM FRANCIS RIENHOFF (From the Department of Surgery, the Johns Hopkins Medical School).

This report is based on three patients who clinically had typical cases of exophthalmic goiter. (Five additional cases were subsequently studied with similar results.) In each of these the basal metabolic rate was well above fifty. Iodine had not been administered to these patients in any form. Under local anesthesia, one entire upper right pole of the thyroid gland was removed. Sections from this tissue showed the characteristic microscopic picture of exophthalmic goiter. Lugol's solution was then administered to the patient for two or three weeks. In all cases the patient improved markedly, pulse and basal metabolic rate becoming normal. Double partial lobectomy was then performed. The portion of the thyroid gland removed at the second operation was compared grossly and microscopically with the portion removed at the first operation. The following changes were found to have occurred during the administration of iodine:

The thyroid gland had increased in size; it had become more hard or rubber-like in consistency and nodular in contour. Vascularity was decreased; collapsed and thrombosed vessels were found. A corresponding disappearance of thrill and bruit at the poles was observed. There was increased scarring as well as increase in fibrous stroma of the gland. Colloid was markedly increased in amount and density. Involutional sequelae were recognized in the form of large colloid cysts, localized and encapsulated, dilated colloid acini resembling so-called colloid adenomas. Transition was found from high columnar to flat or low cuboidal epithelium. Active epithelial cells, before iodine was given, contained large vesicular nucleus, colloid-like droplets, and cells were bulging with contents. After administration of iodine, cells were shrunken, with pyknotic nucleus and no colloid. Acini, papillomatous and lacelike before iodine, later appeared more regular in contour and distended to maximal capacity with colloid. Mitotic figures and epithelial desquamation had disappeared.

Iodine produces an artificial clinical remission in cases of exophthalmic goiter, which is accompanied by a change in the histologic picture from a hyperplastic to a colloid state. The latter, therefore, clinically as well as histologically, is less active than the hyperplastic state. A clinical remission, artificial or natural, is associated with a change in the histologic picture from a hyperplastic to a colloid state. There may be enough hypertrophy and hyperplasia remaining after the clinical remission to characterize the tissue histologically as exophthalmic goiter, but when compared with the same gland before the remission it is evident that relatively the histologic hypertrophy and hyperplasia are markedly less. The degree of hypertrophy and hyperplasia present depends on the clinical course of the disease, in regard to the remissions and exacerbations, either natural or artificial. Involutional sequelae, resembling histologically certain benign tumors of the thyroid gland, occur following an artificial remission, that is, so-called colloid adenomas, colloid cysts, and unencapsulated areas approximating fetal adenomas. The latter areas are usually delimited by the normal lobulation of the thyroid gland.

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, Dec. 14, 1925

RUTH TUNNICLIFF, M.D., *President, in the Chair*

THE MEINICKE MICROREACTION IN SYPHILIS. ANNYMARIE SAUNDERS.

This paper is published in full on pages 388 to 390 of this issue.

FAT REPLACEMENT OF THE GLYCOGEN OF THE LIVER AS A CAUSE OF DEATH. E. R. LECOUNT and H. A. SINGER.

The complete article is published in ARCH. PATH., January, 1926, pages 84 to 92.

THE RESULT OF MECHANICAL OBSTRUCTION OF THE HEPATIC VEINS. J. P. SIMONDS and W. W. BRANDES.

A method of mechanically constricting the hepatic veins in the dog by means of a rubber tube was described.

Such mechanical constriction caused a sudden fall in arterial blood pressure and a simultaneous rise in pressure in the portal vein. Complete occlusion of the hepatic vein reduced the systemic blood pressure by from 37.5 to 42 per cent; maintaining the occlusion for five minutes or more did not cause a continuous lowering of pressure. On release of the constriction, the arterial pressure rose abruptly to a level 10 to 20 mm. of mercury above the original normal level, and then quickly fell to normal.

Complete occlusion of the hepatic veins during peptone shock caused only a slight further lowering of arterial blood pressure. The injection of peptone while the hepatic veins were occluded resulted in a rather marked further fall in blood pressure due to the dilation of the peripheral vessels by the peptone.

Injection of a foreign serum into a sensitized animal while the hepatic veins were occluded did not result in anaphylactic shock; but, on release of the constriction, the pressure rose quickly to normal and then fell precipitately from anaphylactic shock. When the foreign protein was injected while the hepatic veins were completely occluded, after an interval of one-half to one minute the constriction released for half a minute, and again brought about, the resulting fall in blood pressure was greater than that caused by the occlusion of the hepatic veins alone.

Constriction of the hepatic veins caused a marked increase in the outflow of lymph from the thoracic duct.

A Simplified and Quantitative Abderhalden Reaction. F. L. Pickof.

The cumbersome and unreliable method of separating the protein split products by dialyzing shells is eliminated. Instead, sterile test tubes are used. Serum and the substrata prepared from placenta, testicle, or carcinoma tissues are placed in test tubes and incubated for twenty-four hours at 37 C. To each tube is added 10 volumes of 97 per cent alcohol. All proteins down to the proteoses are precipitated, while the protein-split products, such as the peptones, polypeptids and amino-acids, as well as the secondary proteoses, remain in solution. The precipitate is coagulated by boiling for one minute, and the fluid filtered. The absolutely clear filtrate from each tube is then tested with ninhydrin. The intensity of the reaction in the tube which contained the placenta substrate is determined by comparing it colorimetrically with the fluid from the tube with the carcinoma substratum as a standard. In pregnancy the reaction with the placenta substrate is from three to five times as strong as with carcinoma substrate.

AMERICAN ASSOCIATION FOR ADVANCEMENT OF SCIENCE, SECTION N (MEDICAL SCIENCES)

A. J. Carlson, Vice President and Chairman; W. G. MacCallum, Retiring Vice President; A. J. Goldport, Secretary

Kansas City, Mo., Dec. 30, 1925

DISCUSSION OF MEDICAL ASPECTS OF ANIMAL PARASITOLOGY IN JOINT MEETING WITH AMERICAN SOCIETY OF PARASITOLOGISTS

A Survey of Our Present Knowledge of Filtrable Viruses. Vice Presidential Address. W. G. MacCallum, Johns Hopkins Hospital.

The term filtrable virus is strictly applicable to only a part of those living causes of disease which do not fall into the groups known as bacteria, protozoa and higher animal and plant parasites. Of this complex and heterogeneous group the spirochetes are now fairly well known, recent studies of the Rickettsias having thrown much new light on their relation to disease; the group of organisms causing such diseases as smallpox and vaccinia have received some attention, and concentrated work has been devoted to the viruses of the poliomyelitis-encephalitis-herpes group. Of all the other diseases of man, animals and plants which are known to be infectious but in which the causative factor is not yet known, little or nothing has been added to the recognition of the filtrable nature of many of the viruses.

Although the rôle of the leptospira in causing yellow fever is generally accepted, the specific relation of the virus to one kind of mosquito and the time required for what may be a part of the life cycle of this virus in the mosquito before it is able to infect another person, make one somewhat doubtful.

Various Rickettsias which are minute granule-like organisms found in the tissues of ticks and lice have been demonstrated fairly satisfactorily to be the cause of typhus fever, trench fever, Rocky Mountain spotted fever and heart water in sheep. This seems also to be true of the Japanese tsutsugamushi disease. These organisms are not filtrable but are specifically related to the diseases and to particular insect vectors, and their relations are confirmed by the immunity which they leave behind them.

The minute granules found in the eruption in smallpox and allied conditions have been separated and shown to be the cause of the disease by investigators working with vaccinia. They go with difficulty or not at all through filters but can be cultivated together with living tissue in vitro. Their immunologic relations have long been known, and the diagnostic significance of cell inclusions associated with them is familiar, although the nature of these inclusions in these as in other diseases of the great group is unknown.

In the poliomyelitis-encephalitis-herpes group the study of the filtrable poliomyelitis virus and its transmission to animals has long been fairly complete. Little confidence is placed in the results of recent efforts toward the demonstration of the virus of epidemic encephalitis, and it is thought to be entirely unknown. On the other hand, it has been shown that a virus can be recovered from herpes simplex which will infect rabbits, producing in them herpes and a fatal encephalitis — probably the supposed successful demon-

strations of a virus in epidemic encephalitis are instances of accidental infection with the herpes virus. Such a virus has not been satisfactory shown to exist in the virus of herpes zoster, although some authors have claimed its transmission and have even gone so far as to state that its inoculation into children will produce chickenpox, and that there is a close immunologic relation between these conditions. Others, however, as stoutly deny that herpes zoster and chickenpox are identical, and indeed the evidence is far from being sufficient to convince one of any such thing.

Warts and molluscum contagiosum have been transmitted by a filtrable virus, and so have common colds. Influenza is apparently of a similar nature, although this has not been demonstrated; so is rheumatism. Secondary infections have clouded the issue of these studies, and the lack of susceptible animals has made the proof of the nature of the latter diseases difficult.

Dengue is shown to be due to a filtrable virus which is transmitted by *Stegomyia fasciata* and not as was once thought by *Culex fatigans*.

Scarlatina seems to have been removed from this class of diseases by the work of Dochez, Dick and Dick, who think it due to a special form of streptococcus which produces a toxin and leaves an immunity. Their immunologic and therapeutic experiences are nearly convincing, but conservative minds are hard to move from the idea that the streptococcus is a secondary invader, much as the hog-cholera bacillus is only an associated organism in a disease of swine caused by a filtrable virus. Measles is shown to be transmissible to man and animals by filtered blood or nasal secretion. Caronia has found filtrable organisms which he can cultivate in both scarlet fever and measles, but others still regard this with reserve.

Kermorgant has found that mumps is due to a spirochete with an associated bacillus like organism, but that too remains to be confirmed.

One is left with the feeling that in comparison with the amount of published work very little has been accomplished. From a purely intellectual point of view we wish to know everything about the morphology, life cycle and reaction to environment and host of these organisms. If we could know the life cycle as we know that of the schistosomes or of the malarial parasite, we might feel content. From the practical point of view we are more or less satisfied to know merely that in the life history of a filtrable virus there is a point at which its transmission may be attacked and interrupted, as is done when we prevent *Stegomyia* from access to yellow fever patients, and thus exterminate the disease. From this practical point of view immunologic relations assume an importance far out of proportion to their interest from the other standpoint, and practically we can protect individuals from many of these diseases and prevent their spread.

One has the impression that progress is slow because we still use blindly the methods of investigation worked out for bacteriology. When someone offers new conceptions and on them bases new methods of study we may learn rapidly. It seems possible that totally different mediums may be necessary for the cultivation of these organisms, and that different principles of immunity may prevail. One organism properly worked out should serve as a model for all the rest. It is intriguing to reflect that while we know of the existence of only those filtrable viruses which produce diseases, there are doubtless millions of such minute living creatures round about us which will forever escape our perception.

THE QUESTION OF TYPES AND MOSAICS IN THE INTERPRETATION OF HUMAN DIFFERENCES. C. H. DANFORTH, Stanford University.

An analysis of human races and types leads to the conclusion that the foundation on which similarities and differences rests is primarily a genetic one. Endocrinology, apart from genetics, cannot adequately account for the characteristics of various groups of men. A detailed comparison of racial differences and sexual differences shows that these are essentially of the same nature. Men of diverse races differ from each other in much the same way as do men and women of the same race. Sexual dimorphism is known to be due to differences in the gene balance, and the same is presumably true of racial differences. Analysis of various traits indicates that the individual is genetically a mosaic, and, strictly speaking, individuals belong to the same race only to the extent to which they have similar genes. From this point of view, very few people, with the exception of occasional pairs of twins, are of precisely the same race. There are numerous factors, however, which tend to result in certain combinations — types — occurring more frequently than others. These factors are in part understood, but on this aspect of the question much still remains to be done.

THE FATE OF BACT. TYPHOSUM AND OTHER ORGANISMS IN A SEGREGATED VEIN AND IN THE GENERAL CIRCULATION OF THE NORMAL AND THE IMMUNIZED RABBIT. RALPH C. MILLS and GAIL M. DACK, University of Chicago.

The bacteriologic literature of the latter part of the last century is replete with publications dealing with the disappearance of bacteria in the blood stream and with the mechanism by which the animal body is able to rid itself of induced infection. The humoral and the phagocytic theories were in active competition for supremacy in this field. In later years immunologists admitted the validity of both points of view, and now consider that both factors operate in the destruction of bacteria accidentally or intentionally introduced into the body. Humoral destruction of bacteria is still vaguely understood, while phagocytosis is more tangible, and has grown to be more universally believed in as the most important factor in the cleansing of the blood stream of extraneous materials.

By a special technic it has been possible to estimate for the first time the relative importance of these two factors, the results of which lay emphasis on the humoral constituents. The rate of destruction of bacteria in the general circulation has been measured, as compared with the disappearance in an isolated segment of the inferior vena cava left in situ, the blood in which was prevented from clotting by the use of heparin. Heparinized blood, serum and Ringer-Locke's solution were the controls in vitro. The rate of destruction was measured by applying the formulas for the monomolecular and the bimolecular equations, thus bringing it into relation with known chemical reactions. All mediums, except the general circulation, conform closely to the monomolecular reaction, while only the bimolecular equation fits the data derived from examination of the circulating blood.

By comparing the elements present in the various mediums, it is obvious that the only constant but effective factor is the fluid portion of the blood; hence bactericidal action appears to be a function of the physical elements present.

The rate of destruction in the general circulation is much more rapid than in the segregated vein, the only difference between the two being the integrity

of the agglutination-filtration-phagocytic mechanism in the former. Its conformity to the bimolecular reaction curve, while the blood in the segregated vein follows the monomolecular equation, indicates the potency of two factors in one and of a single factor in the other. The difference is believed to be the measure of the phagocytic power of fixed tissue cells.

The rate of destruction varies for various organisms, but the curve corresponds to the same equation, regardless of the conditions imposed. This explains the divergent results of previous investigators.

THE IMMUNOLOGIC BASES FOR DIFFERENT TYPES OF PROTOZOAN INFECTIONS.
By W. H. TALIAFERRO, University of Chicago.

In certain of the trypanosome and malarial infections in which the parasite can be found in the peripheral blood of its host and its course of infection followed, it is possible to correlate the different types of infection with the production of antibodies or reaction products by the host. Types of infection, in this connection, are ascertained by making daily number counts of the parasites per unit volume of blood. Furthermore, for purposes of convenience, the present discussion is limited to those types of antibodies and that type of resistance which exert a directly detrimental influence on the parasite after it has successfully invaded its host.

With resistance used in this sense, if a protozoon successfully invades a host and no resistance is operative against it, it should increase steadily and uniformly in the blood until the death of the host. As soon, however, as the parasites fail to show such a constant rate of increase, some type of resistance may be inferred to be operative which is affecting them adversely. Such an adverse effect on the parasites, with its corresponding effect on the number curve of the infection, can, however, be brought about by two entirely different mechanisms. The parasites may be killed after they are formed (parasiticidal effect), or their rate of reproduction may be retarded or inhibited. The author and L. G. Taliaferro have been able to differentiate the two types of effect by developing a measure for the rate of reproduction of the parasites which is independent of the number of organisms which may be killed as a result of parasiticidal antibodies. By means of these methods three different types of infection are recognized in the trypanosomiasis of experimental animals. These are given below with a short notation of the type of antibody which is associated with each type of infection.

1. When the pathogenic trypanosomes which produce disease in man and animals are grown in the mouse, the host acquires no appreciable resistance affecting either the rate of reproduction or exerting parasiticidal effects on the trypanosomes. As a result, in this host, the infection is of a continuous progressive type during which the parasites increase in the blood at a uniform rate until the death of the host.

2. When the same pathogenic trypanosomes are grown in the guinea-pig, dog, etc., there is no effect on the rate of reproduction, but there are periodical parasiticidal effects resulting in the sudden destruction of the parasites in the blood (crises). These parasiticidal effects have been shown by a number

of investigators to be associated with the production of trypanolysins on the part of the host. The formation of a trypanolysin rarely if ever sterilizes the host, because a few parasites remain which become resistant to the antibody and, as their rate of reproduction is unaffected, can repopulate the blood stream to produce a relapse.

3. In infections with the nonpathogenic *T. lewisi* in the rat, resistance manifests itself both in parasiticidal effects (number crises) and in the inhibition of reproduction of the parasites. The parasiticidal effects may be due (at least in the termination of the infection) to trypanolysins. The inhibition of reproduction is the result of the acquisition of a property by the immune serum which prevents cell division of the parasites, but which does not kill them.

Among the malarial infections, only the infection of birds (*Plasmodium relictum*) has been studied in detail. Here a marked parasiticidal effect of resistance is manifested both at definite number crises and throughout the latter part of the infection. This is, however, not associated with any inhibition of the reproduction of the parasites. The immunologic basis for the parasiticidal effects are not definitely known.

RECENT DEVELOPMENTS IN THE FIELD OF MEDICAL ENTOMOLOGY. W. A. RILEY, University of Minnesota.

From the increasing literature on medical entomology there stand out a few lines of work which have yielded especially significant results within the past year.

The most active work is that relating to kala-azar and other forms of leishmaniasis. In India, Africa, South America and Asia, wherever kala-azar, infantile leishmaniasis, oriental sore or other types of the infection prevail, attempts are being made to solve the problem of the mode of transfer of the causative organism. In northern China, where from an economic point of view kala-azar is in some sections the most important of all diseases, the China Medical Board for two years has had a special field commission at work. So important have been the results to date that the work is to be continued for a third year. In the meantime, an English Commission, headed by Dr. Patton and Dr. Hindle, has just taken up the problem in the same district.

Great impetus to the study has been afforded by the recent discovery that the hamster, *Cricetulus griseus,* a field mouse common in northern China, is susceptible to the disease. The ease with which it is infected, and its ability to withstand the increasing intensity of the infection make it an deal subject for experiments on insect transfer of the disease.

The long accepted idea that kala-azar is carried by the bedbug apparently has proved untenable. Suspicion is now directed particularly to the sandflies, or phlebotomus flies, minute hairy gnats a tenth of an inch or less in length. Improvements in the technic of rearing and handling have rendered possible extensive experimental work with these insects. There is strong indication that they are carriers of both the systemic and the cutaneous types of leishmaniasis.

In connection with this matter should be noted the work of Noguchi, 1924, showing that *Leishmania infantum* is serologically identical with or closely allied to *L. donovani* of kala-azar.

The idea that the occurrence of leishmaniasis in man is due to the more or less accidental transfer of insect flagellates is an intriguing one which has

been the cause of much speculation and experiment, the results of which are still conflicting.

Drbohlav, 1925, in his attempts to inoculate *Crithidia* of the water-strider and *Herpetomonas* of the flea and of muscid flies had wholly negative results, and concluded that there is no etiologic relationship between these three flagellates and leishmaniasis. These results agree with those of Becker, 1923.

On the other hand, Fanthan, 1925, demonstrated before the Royal Society of Medicine a blood smear from a rat which, under rigid precaution to avoid error, he had infected by intraperitoneal injection of *Herpetomonas muscae-domesticae* in the form of an emulsion from the gut of a housefly. A few young, developing forms were seen in ear blood on the ninth day and possible sparse infection on the twenty-fifth day, but on the thirty-fifth day the infection fulminated. The parasites were not seen afterward, in spite of daily examinations up to 315 days.

Interest in the flagellates of plants and their insect hosts continues unabated, and there have been notable contributions along this line, which cannot be included in the scope of this review. Various attempts to determine by direct inoculation the possibility of the development of these flagellates in animals have been frustrated, as in the experiments of Bruni, 1925, by the toxic properties of the latex.

The problematic rickettsia bodies have now been noted in over 50 different arthropods, chiefly insects. Of work on rickettsias pathogenic to man there should be cited the work of Spencer and Parker. In 1924, these investigators showed that guinea-pigs may be vaccinated successfully against Rocky Mountain spotted fever by injections of phenolized emulsions of tick virus. They have since reported that this virus will protect monkeys, and suggest that it will confer immunity on man. In one human case contracted subsequent to vaccination, the course and outcome of the disease were apparently modified by vaccination. Similar work was reported by Breinl, 1924, who conferred immunity to typhus by the inoculation of laboratory animals with an emulsion of crushed, infected lice.

Renewed interest in the possibility of cancer being due, in some cases, to the presence of parasitic worms, has been aroused by the several papers of Sambon, 1924, who, to say the least, leaves the cockroach in an undesirable light. Since the work of Fibiger, 1911, it has been recognized that the roundworm *Gongylonema neoplasticum*, which undergoes an essential part of its cycle in cockroaches, is able to induce a carcinoma of the stomach in rats. Yokogawa, 1925, describes a second species, *G. orientale*, which causes the same effects in rodents. He found the larval stages of the worm in cockroaches in Formosa. This brings the list of animal parasites infesting these household pests up to about forty species.

The work on sleeping sickness and other tsetse fly borne diseases, which was to some extent interrupted by the war, is being pushed with vigor, the more so because there is fear that the movement of the people during the war may spread further the area of human infections. Significant results in control have been effected by Swynnerton in educating and enlisting the enthusiastic cooperation of the natives in the fly area of Shinyanga, Tanganyka Territory. Reports of successful results from breeding and liberating parasites of the fly are yet to be evaluated.

While important world-wide work is being done on the malaria problem, there have been no especially striking results in recent work. With the increasing use of artificially induced malarial infections in the treatment

of paresis, a question of much interest and of practical importance has been raised regarding the possibility of successfully treated patients becoming carriers of the malarial organism. As such they might handicap control measures where malaria is endemic, or become foci of infection in non-malarial regions where the anopheles mosquitoes occur.

Barzilia-Vivaldi and Kauders, 1924, claim that old strains used for direct inoculation become gametocyte-free and hence noninfective to mosquitoes. Two strains which they were using had passed through, respectively, ninety-five and eighty-two experimental inoculations in man, and are said practically to have lost all sexual forms. This claim is at variance with the established facts regarding the cycle of the malarial parasite, and is insufficiently supported by the evidence presented.

Dengue fever has been shown conclusively to be transmitted by the yellow fever mosquito, *Aedes aegyptica (Stegomyia calopus)*. Siler, Hall, and Hitchens, 1925, using bred mosquitoes and carefully screened wards obtained positive results in twenty-five of forty-two cases. In striking similarity to yellow fever, dengue is transmitted to the mosquito during the first three days of the disease, undergoes an incubation period of eleven days, and the insect is probably infective for the remainder of its life.

DEVELOPMENTS IN ANTHELMINTIC MEDICATION. MAURICE C. HALL, Washington, D. C.

The subject of anthelmintic medication has undergone an evolution which may be divided into three phases. The latest phase covers about a decade, the preceding one about half a century, and the earliest covers the many centuries back to historial obscurity.

The first phase covers the long period of uncritical empiricism. This phase doubtless had its obscure beginnings in the observations of early primitive savages, if not of prehistoric man, when the passage of such large worms as ascarids was noticed and this passage associated, in the course of time, with certain foods and other substances eaten. From the nature of things, plant material would be suspected of causing the removal of the worms, rather than animal or mineral material; most of our present day anthelmintics and almost all of the oldest ones are of plant origin, the oldest now in use, male fern, being known to Theophrastus, Dioscorides and Pliny. The anthelmintics of this period were used because the passage of worms occasionally or frequently followed their use. On this basis scores of substances have been used and are entitled to a status as anthelmintics, but most of them are comparatively useless and valueless.

This first period of anthelmintic medication, with its uncritical accumulation of unstudied anthelmintics of unknown value, drew to a close with the growing interest in hookworm disease following the work of Sonsino and others about 1878. The year 1881 may be taken as the beginning of the second phase of anthelmintic medication, as it was in this year that male fern, thymol and chenopodium were first proposed and tested as anthelmintics for removing hookworms. Male fern had a transient vogue, but was in time replaced by the more effective thymol and other drugs. Thymol held the field for years, sharing it to some extent with betanaphthol after this drug was proposed in 1904. Chenopodium appears to have been discredited by the adverse report on one case by Baumler in 1881, and did not again receive consideration until Schüffner and Verwoort tested it about 1912, following which time it came rapidly to the front as in many respects the best drug for the treatment of ancylostomiasis.

During this second phase of anthelmintic medication there was a growing tendency to test the efficacy of these drugs in some way to ascertain their actual and relative values. The early judgments on these points were made on the basis of clinical improvement and of worms passed. The examination of feces for worm eggs after treatment added some other information of value. Recent developments in the way of correlation of egg counts with worms present by such methods as those of Stoll and Clayton Lane have contributed much to our knowledge, and the standardized test and trial treatments, as developed by such workers as Darling and Smillie, have been of great value.

The methods of test used during this second phase have, however, inherent limitations. They do not give the exact information that is desirable in regard to the important subject of worms not removed by treatment, and as a means of advancing our knowledge in regard to any proposed anthelmintic they are too slow if reasonably elaborate and accurate, and too inaccurate if simple. The desired information can be obtained to advantage only by the experimental method of critical testing on animals, and the systematic use of this method of testing characterizes the third phase of anthelmintic medication of the past decade. In critical testing animals are given measured doses of the drug to be tested, all worms passed for an adequate period are collected, identified and counted, and the animal is then killed and the worms present postmortem are collected, identified and counted. This method gives exact information and permits of experimentation with new drugs and chemicals. Up to the present time the findings on dogs have proved immediately applicable, as a rule, in the field of human medicine.

Critical testing was first approximated by Grassi, Calandruccio and Perroncito in 1884 to 1886, their tests establishing male fern as a satisfactory drug for the treatment of hepatic distomiasis in sheep. Subsequently their findings and their method were neglected for many years. In 1915, thirty years after the Italian work, the late Dr. B. H. Ransom established an anthelmintic project in the Zoological Division of the Bureau of Animal Industry, with the present speaker in charge. This work has been carried on for a decade, and this and similar work by others who took it up during that decade represent the characteristic feature of the present third phase of anthelmintic medication. This work has standardized procedure in veterinary medicine and has established dependable treatments for the many parasitic conditions in which previously the veterinarian had to take his choice of a hodge-podge of drugs of unknown efficacy.

The most recent and striking developments from such experimentation are the attempts to correlate anthelmintic efficacy with chemical composition and with such physical characters as the water-solubility of the drug, the development of certain principles of anthelmintic medication, and the introduction into veterinary and human medicine of two new anthelmintics, carbon tetrachloride and tetrachlorethylene, for removing hookworms. In a series of chlorinated hydrocarbons the anthelmintic efficacy appears to be correlated with the chlorine content. There also appears to be an optimum solubility, not yet accurately ascertained. Carbon tetrachloride, proposed on the basis of experiments on dogs in 1921, appears to have been used in more than 1,500,000 human cases of ancylostomiasis. Tetrachlorethylene, proposed on the same basis in 1925, is already in use in veterinary medicine and is being tested in human medicine.

There are as yet few workers in this field of investigation, but there is evident opportunity and need for much work of the sort. The subject shares the neglect which has been accorded the entire subject of parasitology in the medical and veterinary schools of this country. The investigations are not

confined to the testing of anthelmintics for removing worms from the digestive tract, although most of the work has been done in that field, but extend to the testing of drugs for the destruction of worms in the various tissues and cavities of the body. There are, among the worm parasites of this group known from domesticated and other animals, forms sufficiently similar to those involved in somatic helminthiasis in man to give information which should be applicable, immediately or by modification, in human medicine.

THE CHANGING POINT OF VIEW IN HOOKWORM CONTROL. W. W. CORT, Johns Hopkins University.

Although the main lines of procedure in hookworm control work were laid down early, the investigations of the last few years have produced radical changes in the point of view. A discussion was given of some of the recent discoveries on the epidemiology of hookworm disease and their effect on the control program. The use of the Baermann apparatus, which makes it possible to isolate infective hookworm larvae from the soil, has shown that these larvae do not migrate actively from their place of development and that their life in the soil under tropical conditions is much shorter than was previously supposed. It has also been possible by the use of this method to determine more accurately the conditions in the field which are favorable or unfavorable for the development of the larvae, such as types of soil, protection by vegetation, etc. These investigations have made it possible to predict to some extent at least the danger of soil pollution under different sets of conditions and have helped in the understanding of the sources of infection in the field.

The development of quantitative methods of measuring hookworm infestation has greatly influenced control procedure. Darling's use of the worm count was an important step. Now a simpler technic, Stoll's egg count, is used to estimate the degree of hookworm infection of a population group. By the use of this quantitative measure to replace incidence statistics, it has been possible to gage the relation between degree of infestation and the injury produced. It has been shown that light infestations produce no appreciable injury and that in many places where there is a high incidence of hookworm infestation the average number of worms present is so small that the group cannot be considered as suffering from hookworm disease. In such places the value of control work is limited. By the use of this quantitative estimate in preliminary surveys it is now possible to determine in a given region whether there is sufficient hookworm disease to call for a control campaign, and in what parts of an area the work should be begun. It is also possible to test quantitatively the results of the control work and its permanency by resurveys.

A combination of the Baermann soil survey with the Stoll egg count and careful observations on soil pollution is now extensively used in making epidemiologic studies, which are yielding information on the factors influencing the spread of hookworm disease. Such studies have shown interesting relations between severe hookworm disease and types of cultivation, as in the coffee plantations of Porto Rico and the silk producing regions of China. They are also giving more precise information on the effect of climate, soil and habits of soil pollution on the spread of this parasite.

Gradually the scientific basis on which the hookworm control program rests is being made more adequate, and every procedure is being recast and reevaluated in the light of the newer information. The emphasis has turned away from the complete "cure" of the individual to the rapid destruction of worms by mass treatment until the infestation becomes subclinical, and the effort is to hold it at this level by improved sanitation.

Book Reviews

A Text-Book of Pathology with a Final Section on Post-Mortem Examinations and the Methods of Preserving and Examining Diseased Tissues. By Francis Delafield, M.D., LL.D., Sometime Professor of Practice of Medicine, College of Physicians and Surgeons, Columbia University, New York; and T. Mitchell Prudden, M.D., LL.D., Sometime Professor of Pathology, College of Physicians and Surgeons, Columbia University, New York. Thirteenth Edition. Revised by Francis Carter Wood, M.D., Director of the Pathological Department, St. Luke's Hospital, New York; Director of the Institute of Cancer Research, Columbia University, New York. Price, $10.00. Pp. 1354, with 18 full-page plates and 810 illustrations in the text in black and colors. New York: William Wood & Company, 1925.

This book has an interesting and honorable history. In 1878, T. Mitchell Prudden (1849-1924) began full time service as assistant in pathology and director of the laboratory of the alumni association of the College of Physicians and Surgeons in New York. At about the same time William H. Welch became professor of pathologic anatomy and general pathology in Bellevue Hospital Medical College in New York. Those two were the first in this country to give their whole time and attention to teaching and working in pathology. At the time there was no textbook in English that could be said to do justice to pathologic anatomy as studied and taught especially in Germany. Even before his return from Europe in 1878, Prudden had considered translating a small book by Perls, but he was unable to obtain an American publisher. The need in question was filled by the publication in 1885 of a second edition called "Hand-Book of Pathological Anatomy and Histology," by Delafield and Prudden of Delafield's "Hand-Book of Postmortem Examination and Morbid Anatomy" (1872). A new edition was called for in less than one year. Owing to the clear grasp of the principles and practical details of pathology and its lucid style, this book has held its place as a standard text ever since. The subsequent editions all have been revised with special care, and each became more complete and comprehensive than its predecessors. The number of illustrations has increased regularly; most of the illustrations were drawn by Prudden, and many of these still serve the purpose adequately. With the sixth edition in 1901 the main title was changed to a "Text-Book of Pathology, etc." Dr. Francis Delafield, medical teacher and close student of pathologic anatomy, now no longer shared actively in the revisions. In the preface to this edition it is stated that it has seemed wise now to dwell on the relationships of pathology to the allied phases of biologic science and "to view pathology as one aspect of the diverse manifestations of life and of energy, rather than as belonging to a special and exclusively human domain." The eleventh edition (1919) was revised by Dr. Francis Carter Wood, one of Prudden's pupils. The twelfth edition appeared in 1922, and now the thirteenth edition has appeared.

In the preface Dr. Wood states that his corrections and additions in the last edition concern a few special matters, notably the "reticulo-endothelial system," recent advances in the understanding of certain infectious diseases, abscess of the lung, bone tumors, changes in the views in regard to jaundice. There is an abundance of references to American work in pathology. It seems certain that the book will continue to hold its own as a standard text for general use.

APPLIED BIOCHEMISTRY. By WITHROW MORSE, PH.D., Professor of Physiological Chemistry and Toxicology, Jefferson Medical College, Philadelphia. Cloth. Price, $7.00 net. Octavo. Pp. 958, with 257 illustrations. Philadelphia: W. B. Saunders Company, 1925.

This represents an attempt to combine a systematic treatise on physiologic chemistry with a laboratory manual in such a way as to interest and enlighten specifically the student of medicine. For this purpose it seems well adapted. The relation of the substances under laboratory investigation to vital processes is constantly kept in a prominent place, and the significance of both for medical problems is occasionally pointed out, a procedure that presumably will help to maintain the medical student's interest while he is acquiring the basic facts. Even more medical information might be distributed through the pages to advantage. Much more attention is paid to underlying chemical principles than is usual in laboratory manuals of biochemistry. There is an excessive amount of unnecessary illustration by means of cuts from supply house catalogs. A page of full dinner pails with the lids on seems to lack educational value. As is usually the case with chemists venturing into problems of medicine, there is more credulity concerning the finality of theories of etiology than the hardened medical investigator is willing to exhibit, e. g., the acceptance of the relation of guanidine and methyl guanidine to tetany, or the production of cirrhosis of the liver by proteoses. The pathologist detects occasional errors more noticeable to him than to a chemist, e. g., the statement that hyperthyroidism and hypothyroidism are types of goiter, that hemolysis results from rupture of the stroma, or the use of the term coccus bacillus. The photographs of a number of American biochemists appear for the purpose of familiarizing the student with some of the contemporary leaders in the field, but the omission of some of the leaders from the gallery may serve to mislead the student. The student will also be confused by the adoption of certain standards of chemical nomenclature and the rejection of others, for he will have to learn new words and definitions from his other books — but this is a part of the chaotic condition of the orthography of biochemistry which awaits direct action by constituted authorities. These are minor criticisms. On the whole, the book should be of value to the medical student taking his course in biochemistry.

METHODS AND PROBLEMS OF MEDICAL EDUCATION. Paper. First series, pp. 151; second series, pp. 118; third series, pp. 242. New York: Rockefeller Foundation, 1924 and 1925.

These publications deal with the administration, construction, equipment and maintenance of medical laboratories and clinics. They are issued by the division of medical education (R. M. Pearce, director) of the Rockefeller Foundation. The purpose is to present information in regard to new buildings, methods of instruction and similar matters in convenient form for those interested. The first series deals largely with the teaching of anatomy, and contains articles by European and American anatomists. It contains also an interesting description of the pathologic institute at Graz. The second series, by M. J. Rosenau, is devoted to the discussion of the sanitary survey as an instrument of instruction in medical schools, and contains as a sample a copy of the report of a medical student of his sanitary survey of the city of Rochester, New Hampshire. The third series contains descriptions of departments and laboratories for fundamental medical branches in various places, including the

department of pathology at Western Reserve University, the Senckenbergische Anatomie of the University of Frankfurt; the pathologic institute at McGill, and the new pathologic laboratory at the Johns Hopkins Hospital. From these articles, which are well illustrated, one obtains clear ideas of various special buildings and laboratories. The publications will be of much use to all those who are interested in the construction of new medical buildings and in improvements in the organization of departments of instruction. In the prefatory note, recipients are invited to make suggestions concerning desirable articles and to send names "of those who might be interested either in these collections as a whole, or in 'separates,' representing special fields."